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STUDY OF THE GENERAL DYNAMICS OF THE PHYSICAL-CHEMICAL SYSTEMS IN MAMMALS

by A. S. Iberall

Prepared under Contract No. NASw-1066 *by*
GENERAL TECHNICAL SERVICES, INC.
Cleveland, Ohio
for

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INTRODUCTION

In an earlier study, development of a complex of primitive ideas was begun of how the biological system was coordinated for regulation and control purposes. This material was reported on in three reports (1). In the present study, this work was continued. A moderate difference in emphasis has developed. The previous study visualized investigating four isolated systems -- the temperature regulating system, the cardiovascular system, the hormonal system, and the behavioral system. However, the ideas behind these systems have tended to coalesce to a related pattern of dynamics systems analysis. Thus in the present study, while the same four systems will be kept in mind, the attempt will be made to emphasize the fuller nature of the physical dynamics used by the macroscopic system.

The work of another investigator, Goodwin (2), has just come to our attention. His book attempts a serious beginning of the microscopic dynamics of the biological system at the cellular level. Any reader of both references may note the large degree of parallelism of ideas. These efforts are thus mutually reinforcing, and not isolated, but the product of the scientific view that has evolved in the past 40 years that systems may be viewed and analyzed usefully by their dynamic properties, that is by their spectral properties. It is the product of the physical age, and is worthy of note until it either produces significant results and should be taken over as a working methodology, or it falls on its face and should be discarded. We hold no brief for either end, but simply propose to continue work until either one or the other conclusion seems possible.

TOWARD A NEW DEFINITION OF LIFE

The purpose of this section, not metaphysical, is to attempt a useful operational definition that may redirect biological attention to a view of life that is perhaps physically useful.

The usual definition of life (Haldane, or Oparin are classical sources; or (3) contains other references) seems to mix a performance and a materials specification. It generally requires that a complex system of organic reactions are involved in such processes as self-locomotion, metabolism, reproduction, and growth. Yet the definition does not supply sufficient clue on how to build a living system, or if one builds a system, when does it have sufficient properties to begin to consider it living. Furthermore a most significant property of living systems -- viability, i.e., the ability to move, squirm, and adapt to the local milieu -- does not seem contained in its definition.

In the previous study (1), the living system was finally viewed as a bound together collection of oscillators (synonomous terms are oscillators, engine cycles, clock cycles, D.C. - A.C. convertors, biological rhythms). This now begins to emerge as the most likely significant element in leading to a definition of life, as the following discussion may clarify.

Consider a passive block of material (its internal oscillator molecular structure will be disregarded at the present). This has no 'living' properties. Consider next, one step higher, a watch. This now contains one oscillator. To an elementary mind, there is already an active 'beating' element that vaguely resembles life. Put such a single engine oscillator element into a car; connect it to a transmission, and a locomotory system; declutch the transmission, and couple the gas pedal and wheel to any algorithm, even a random one; and let the automobile go. The resemblance to a life form has increased. Increase considerably the number of oscillator elements, the coupling to locomotory systems, and the complexity of algorithmic content and the resemblance to a living form becomes increasingly great. This is proposed as a main line of biological thought.

Thus life is tentatively defined as any compact system containing a complex of sustaining non-linear limit cycle oscillators, and a similar system of algorithmic guiding mechanisms, that is capable of regulating its interior conditions for a considerable range of ambient environmental conditions so as to permit its own satisfactory preservative operation; that is capable of seeking out in the environment and transfering and receiving those fluxes of mass and energy that can be internally adapted to its own satisfactory preservative operation; that is capable of performing these preservative functions for a reasonably long period of time commensurate with the 'life' of its mechanical - physical - chemical elements (i.e. clocks made of parts that should wear for hundreds of years that run for two seconds are not crickets); and - likely as a luxury part of the definition - that are capable of recreating their own system out of materials and equipment at hand (one will have to note in the future how much of the biological system can be rebuilt, or one can recall the story of the amorous young bridegroom who has watched his bride remove most of her apparent charms before his eyes - teeth, eyes, hair, wooden leg, etc.).

The purpose of this definition is to guide the physical search for 'explanations' of the operation of the biological system; and to leave the physical scientist closer to some physical base by which he can model, 'build', or assess systems that resemble naturally 'living' systems by suitable operational definitions; and a clue that 'life' does not have to be explained by only one mechanistic scheme per system, but may involve many possible types of successful operation.

THE TEMPERATURE REGULATING SYSTEM

In the previous study (1), what has been demonstrated and discussed is the existence of limit cycles of 90 ± 30 seconds; 400 ± 150 seconds; 1400 ± 400 seconds; 4000 ± 1500 seconds; 12,000 ± 3000 seconds. It was proposed that the first is an engine cycle; the second a blood flow vasomotor cycle, likely for heat exchange regulation; the third gas storage in the tissue (CO_2); the fourth not known (although perhaps also involved in gas storage time delays); and the fifth from heat storage in the body due to its overall massive capacitance lag.

It is not implied that the spectrum is sharply monochromatic at each of these periods, or even sharply stationary. However, it is implied that there is a considerable power density piled up in each of these regions, and that therefore there are specific mechanisms at work in each salient region. The continued concern will be predominantly with the 'high frequency' 100 second cycle.

The data in the third report of the previous series indicates that this limit cycle can be demonstrated at least in the ventilation rate, the internal and surface temperature changes, and in the heart beat rate. Considerable discussion of one gas storage model (4) was carried out. It was tentatively

decided that the model was inadequate to explain a power production cycle, as a variation in metabolism or the variation in temperature would imply, and that the physiological linkage must be hormonal. By hormonal was meant a small concentration chemical messenger which would require the blood system as its carrier, and which was generated likely at some other spot that the local site. In order not to miss any possibilities, some tentative arguments will be given to include the possibility of local site chemical mediators, although a central coordination of the overall power production is necessary.

Thus the present concern must begin at the local — not quite molecular — level, i.e., at the level at which a physical 'cell' can be thought of to exist, as far as equilibrium is concerned. Since the cycle involves the delivery and storage of fuel, the supply of oxygen, catalysts, enzymes, possibly local hormones, and the carriage of waste product, the 'cell', like a crystallite domain in solid state physics, must involve a considerable number of biological cells and pieces of systems. Specifically it must include the chunk of the proximal blood system that supplies the region.

Classically explanation at this level may be viewed first from the pioneering works of two such men as Krogh and Lewis (Krogh references Ebbecke as the pioneer). As was finally uncovered in the third report of the previous series, it is likely Lewis, who by direct microscopic observation of limited regions was able to demonstrate an ever-changing dynamics of blood flow at the 1-2 minute level in the small artery - arterioles - capillary - venule - small vein system. While it is common to discuss arteriovenous anastomoses (shunts of the capillaries from arterial to venous side) as well demonstrated in rabbit ear and dog paw, and only postulated in the human extremities (see for example, Best and Taylor (5), pp. 345-349.) the entire skin color system developed by Lewis by his painstaking observations demonstrates the reality of blood pulsing in the local blood supply, and likely of the time domain of effect here being sought. On the other hand, a possible capillary twinkling appears to be of a much higher frequency level (10 cps) and related to oxygen distributions in the surrounding tissue. Further, since the previous report showed the involvement of heart rate at the same minutes periodicity, the local blood pulsing oscillators cannot be independent, but must be at least partly correlated. Thus the cycle has not been explained at this point. Instead the numbers of elements that are involved has been increased.

What is a vague orienting thought is that while the system as a whole has negligible oxygen storage, it is possible that the oxygen distribution at the highest frequency rate, provides a lively adjustment system capable of quickly modulating the blood distribution system into a 'best' distribution for spreading the oxygen around; that the next time domain, centered around 1 cps and extending to 10 cps and 0.1 cps represents much of the heart pump - distribution system operating band; and that finally an oxygen supply in the blood inadequate to supply all of the active muscle 'engine' sheath becomes involved in an unstable equilibrium situation in which there is local oscillation in one region as compared to another. This latter thought is worth some further discussion.

As a first approximation, the blood is charged up in the pulmonary circulation to a near constant partial pressure, and the arterial system supplies the capillary beds with a near constant flow. A possible high frequency twinkling (10 cps) of capillary blood supply assures an approximate local constant vascular oxygen content through whatever mechanism strips the oxygen from the capillaries. Now the stage is set for the instability.

If one postulates that the muscle sheath is marked by being an unstable system then the system can be made to work. It requires:

a. That the muscle cells, as an assembly, are the only unstable metabolizing system (as compared to the other cells).
b. That the muscle cell instability tends toward maximizing its oxidation rate (It is this unstable characteristic that makes the muscle system likely ready to adjust to any demand).
c. That the potential oxygen flow capacity is limited by it arising from a fixed potential (oxygen partial pressure) source through a variable resistance with a certain limiting minimum resistance (The 'resistance' is posed by some transfer membrane).

Now the ingredients are set for the unstable action.

In some particular region, which may even be a preferred region (remembering that the problem at hand is to account for the engine cycling in a distributed system), the local cooperative muscle motor units start to leach out the oxygen from their capillary supply bed. This depletes the local supply and for unexplained reasons (likely a local chemical reaction, so that the 'hormonal' concept is here reduced to a local chemical chain), the reaction is inhibited. In some other region, then, other motor units start to pick up.

It is likely that there is a preferred 'firing' order as the wave of demand 'diffuses' through the system. The preferred order can likely depend on the individual - how his musculature is developed; his posture; his activity; his recent history - what residual settings have been left in the distribution system from its past recent thermal status, recent food status, recent excretion status, recent activity status, recent emotional status. It develops the 'weakness' that one might find in a two lobed balloon in which one or the other lobe may be the first to blow up; or in the firing order of a ring oscillator. In extremely high quality or perfectly designed rings, one may get a very rigid firing order. However in more rugged, and adaptable rings, the firing order may only be broadly statistically determined. A non-stationary character is thus quite reasonable.

The essential element is the muscle instability. The vague general evidences for this are precisely the existence of high frequency sustained jitter in muscles; the muscle discharge patterns of heat - and therefore oxidation cycles - known since Volta's time, and so well exposed by Hill; the spastic, aphasic, and other muscle instabilities in disease, in paraplegics, in ordinary people under particular conditions -- all of these point to a system which becomes unstable with some opening or modifying of the state of the loop. In fact it was a search for a similar instability that Wiener describes as leading him to his key idea of feedback in biological systems in cybernetics. Another possible indicator of instability is the convulsions produced by exposure of the system to high oxygen total pressure. This bears evidence that the center of instability lies in the nervous system. (As is the case in the pacemaker cells in the heart). An alternate is that there is an internal instability which is discharged by nerve stimuli or by a chemical. (See adrenalin in hormone section).

Such instability can create the equivalent of bistable or unstable states. The missing ingredient is the timing phase. It is common in non-linear systems that the frequency in a non-linear limit cycle, operating in a relaxation mode, or between bistable states can be determined by an R-C time constant or

an L-C resonator period (See for example discussion in Minorsky (6) or background discussed and documented in part in background in (7)). Nominally, the two states, plus a resonator or time delay element can then determine the interval to the next switch state. In the internal combustion engine, the rotating flywheel determines the time element that carries the system to the next power impulse phase.

The chemical view of the problem of creating local chemical oscillators is much more horrifying than the simple physical view of requiring the oscillator. A number of modern ideas and the present state of the physical modelling now remove some of the pain. It has gradually become apparent that the system actions must be closer to what is common in man-made physical-chemical systems, in which the cycle is created chemical-mechanically. The modelling now proposed is an unstable chemical 'engine' cycle which is 'choked' in its oxygen supply. Whereas in man systems it is common that time delays are obtained mechanically or electrically, here it is no longer so difficult to obtain a chemical time delay, and a saturation property. The local function proposed is validly called hormonal, with the basic implication of it occuring at small signalling concentrations.

The proposed, but still vague, model is viewed in the following context:

An essential ingredient is that the rate determining reaction is a local cycle with about 100 seconds lag. The system is coordinated by a limited flux of constant potential available to support the oxidation.

Now just as a ventilation cycle was found by Adrian in the isolated brain stem, and which may then be mediated in frequency by other input signals; and similarly in the heart; a basis for a similar proposal is found for the muscle 'engine' cycle. There may very well be a near unstable oscillator or a periodic cycle involving the respirator center and aorta chemoreceptor. (Thus reconciling a view with (4)). They may very well involve time lagging processes to the sensors. However, it is proposed that the major engine cycle involves oxygen use. The 100 second time scale should show itself as a slow pulsing of the oxyhemoglobin-carboxy-hemoglobin interface in the capillaries. This advancing-retarding front is the equivalent of an effective surface area available for the oxygen exchange.

Whether the rate governing reaction - always assuming the muscles to be unstable - is a local chemical chain or a physical diffusion time constant is at the moment only a detail. (Rushmer (8) p.11-12, mentions 1948-1949 work of Flexner et al, establishing exchange rates of the order of 60% per minute for small ions and molecules from capillaries; and work of Pappenhauer et al in 1951 as establishing possibly even faster rates). The main element in the concept is to show that the cycle may exist in the oxygen content of the capillaries. The region is so rich in exchange area that the control of oxygen 'diffusion' into the tissue must come from and can easily come from this region.

Casting through some standard texts show that though there is some apparently contradicting opinions, there is a thread of agreement with the major thesis laid down here. Thus Guyton (9) points out "prolonged stimulation of a motor nerve at high rates will progressively diminish the quantity of acetylcholine secreted by the end-plate, which causes more and more diminution of transmission into the muscle fibers. This is called fatigue of the neuromuscular junction. This effect is quite different from transmission of impulses in

nerve fibers, for fatigue of nerve fibers to the extent that conduction is impaired is almost unknown under physiological conditions." 'High rates seem to mean rates higher than normal stimulation for earlier "stimulation at rates greater than 150 times per second is likely to diminish the quantity of acetylcholine..."). Yet Rushmer (8) points out (p. 100) that fatigue in muscles after exhausting exercise "does not result from the accumulated products of metabolism", for electrical stimulation at a point over which a motor nerve enters a muscle will produce the same power of contraction in a 'fatigued' muscle as in a fresh muscle.

The reconcilation of all such somewhat conflicting views lies in deciding upon the rate governing reaction. What Rushmer is saying is that at ordinary repetition rates - which might be up to 10 per second in tremor - the contraction of a muscle depends on presence of central nervous signals, not on local fatigue products ("The sensation of 'tiredness' does not even originate within the muscle or the peripheral nerve. The voluntary flexion of the muscle must be interruped by depression or 'fatigue' within the neural chains in the central nervous system"). Thus the activity of the local muscle unit is not governed or inhibited by the products of metabolism in the ordinary range of action. Furthermore, the activity of the local muscle is not governed by central nervous system signal in the ordinary immediate range of action. What these paradoxically put sentences mean is that the second to second adjustment of muscle to load is not governed by fatigue products on one hand - which operate at a slower time domain to influence the action of the system as a whole - nor by electrical control nervous system signals on the other hand - which can turn the muscle on and off but which operates at a faster 0.1 second rate.

(This discussion attempts to illuminate a first question that is faced in considering the problem of the biological system. How does the system operate in a stable fashion with so many coupled, interacting, and competing systems? The answer, gradually evolving in our thinking, is by strict segregation of mechanisms in different portions of the time domain, by fixing the time domain with limit cycle oscillators (namely by 'fracturing' the time domain into preferred weak spots in which to trap salient responses), and by associated related inputs which can mediate limit cycle oscillator stability, rather than by changing mechanisms. Thus the problem becomes the more usual one for the physicist of taking apart the mystery of a frequency spectrum, here the biological spectrum).

Having narrowed the possibilities, there remains only two possible elements in the local domain to mediate the metabolic cycle. One can either make the fuel supply rate determining, or the oxygen supply rate determining (since it is not on-off switching from by-products, and since it still seems likely that once switched on, the rate governing chemical reaction is very fast and uniform). The storage of 'high energy' fuel in the muscle and surrounding tissue is quite high as running isolated muscles demonstrate (i,e. times in the 5-10 minutes range are easily possible), whereas oxygen deprivation, as in the case of high altitude anoxia and death, is in the tens of seconds. Thus it would seem quite reasonable that oxygen availability becomes the rate determining reaction. Oxygen availability, from its very nature of an arterial and a venous subdivision, would seem to require the interpretation that it is represented as an effective area exposed in the capillary bed in oxyhemoglobin rich blood as compared to carboxyhemoglobin. (Just as Gagge introduced the concept of effective wetted area in perspiration). In this regard p. 11-13, and p. 98-101 in Rushmer (8) are very illuminating. In the earlier section, nominal mechanisms for

oxygen diffusion through capillary walls are illustrated. The point here is that regardless of whether the illustrations are exact or not, the oxygen diffusion is proportional to capillary surface area and to the partial pressure available in the blood carrier. Thus there is transfer where there is oxygen rich hemoglobin and less transfer when there is less rich hemoglobin.

In the latter section, it is first pointed out that the capillary area is about 1000 fold greater than the body surface area, and that the cells are rarely more than 0.1^{mm} away from a blood supply area (This already poses the problem, because the surface area of the cells is so much greater than the oxygenating surface area that there is not a free exchange limited by the cell wall but by the rate governing reaction that brings the oxygen through the capillary exchange surface). Rushmer then points out "influenced by common personal experience, we are inclined to view peripheral vascular control primarily in terms of delivery of oxygen to the tissues, as is implied by ..." his figure. In that figure are shown the difference between extraction in inactive tissue (arterial blood entering the arteriole - capillary complex with 19% by volume oxygen, and leaving the venule capillary complex with 17%) and extraction in "active skelatal muscle" (entering with 19% and leaving with 5%). "Tissues which release energy at rapid rates, e.g. contracting muscle, extract a major portion of the oxygen from the blood." (i.e. here shown as approximately 7-fold more oxygen for the same blood flow in two different capillaries.) However, this is precisely the point that was inferred from physical reasoning in the earlier papers in human thermoregulation (10). (It is disconcerting to find the result stated so baldly here because in the past 8 years of seeking physiological comments on this point, it was never clear whether the thought was strange or wrong in physiological eyes. Since the entire nature of human thermoregulation would 'obviously' follow from this point, its importance cannot be overstressed. Furthermore as these earlier papers indicated, it had been inferred from some discussion with a medical collaborator, that the system was not organized into a pure geometric muscular sheath, but was broken into organistic pockets, and that the likely generic term for the 'muscle engine system' alluded to was the entire collection of mesodermic systems, consisting of skeletal muscle sheath, heart, kidney, brain, stomach, etc. On this score the subsequent discussion in Rushmer is significant.). "Oxygen is used at a prodigious rate in relation to the available stores during exertion. When the circulation is restored after occluding the arterial supply to the arm or leg for a few minutes, the flushing of the skin, the throbbing of the limb and the return of the power of contraction all attest to the essential role of the blood supply in the function of muscles and skin. Indeed, this greatly accelerated blood flow (reactive hyperemia) after temporary arterial occlusion is generally attributed to vasodilation induced by depressed oxygen content in the tissues and to accumulation of carbon dioxide, lactic acid and other "metabolites" in the tissues. In addition this mechanism has been widely invoked to explain the vasodilation that produces accelerated blood flow in most regions of the body at one time or another. Actually, the substance or substances responsible for reactive hyperemia has not been identified."

(Discussion follows later on the adequacy of various chemical dilators - ATP, ADP, vasopressin, angiotension, histamine, etc. - to fit in the scheme but without success. "At the present time reactive hyperemia is attributed to vasodilator metabolites accumulated during hypoxia..." but "...the vascular reaction must be attributed to unidentified vasodilator substance."). In the light of his discussion about muscle 'fatigue', it is not clear that a chemical step is needed in the direct causal chain of determining the oxygen flow. This will be touched on again a little later.

Rushmer depicts the normal oxygen blood flow distribution. It is useful to summarize these.

Cardiac output	= 4300 cc/min.
Arterial O_2 content, 19% by volume	= 817 cc/min.
Venous O_2 content, 14.3% by volume	= 615 cc/min.
Oxygen uptake	= 202 cc/min.

Uptake in major elements	Blood flow-cc/min.	Changed Oxygen Content % (From 19% Entrance to Exit)	Oxygen Usage cc/min.
brain	760	6.8	52
heart	225	13.7	31
G-I tract	1155	5.1	59
kidney	1115	1.2	14
muscle	810	5.7	46
skin	215	6.1	13
Total	4,290		215

The high percentage utilization in mesodermic organs is obvious. However, beyond this is the statement that "resting skeletal muscle utilizes only about one-third of the oxygen in the blood it receives, but contracting skeletal muscle extracts about three-fourths of the oxygen from the blood." Thus it is consistent that the heart as a working 'muscle' is tabulated as extracting about 70% of the oxygen but that the resting skeletal muscles are only extracting 30%. The basic issue is how the extraction takes place. The physiological literature is weak in dynamic description. Yet it is clear, here, that the muscles can shift their absorption from 30% to 70%. Much more specific, it is likely that the 'rest' state of the muscle need only absorb the 10% shown in the previous figure for inactive tissue. Thus it is more likely that the dynamic range covers the 10% to 70% range. This would amount to 15 to 100 cc/min. possible oxygen consumption in the contracting skeletal muscles in near quiescence and likely more than double in activity. These numbers by themselves do not mean anything, but they are indicative of the dynamic range of oxygen consumption that might be expected from muscles. They happen to agree in dynamic range with what was found in the human in quiescence in the 1-2 minute cycle (i.e. a near 2-1 running range).

Trace now in a little more detail the need for a chemical vasodilator. In the modelling as done so far, the dynamic regulator or control element is the oxyhemoglobin front in the capillary. Its positioning must be done by control of the arteriole resistance, i.e. the blood flow is locally increased or decreased to maintain the front. The domain of action is the 1-2 minute cycle. This could arise from a local chemical signal, which would therefore lend merit to the standard position advanced by Rushmer of a vasodilator substance. However the actual mechanism has to arise from a high frequency twinkling of capillary opening and closing. Viewed against the background of Zweifach (11), it is likely that this twinkling is under the control of norepinephrine, epinephrine ("the tone of the microcirculation may well be maintained by norepinephrine continuously discharged from the nerve endings, and by the level of epinephrine circulating in the blood"). It is not possible at this time to say what the specific response function that this high frequency hormonally mediated oscillator is performing, but these sources quoted do not contradict Krogh's concept that there is a response to the local tissue gradients of oxygen.

Now a high frequency twinkling must cause a high frequency fluctuation in the oxyhemoglobin (OH) front. This must fluctuate widely in the capillaries. (Stripping the slow velocity front of the order of 0.7 mm/sec. at the 0.1 second level involves fluctuating changes of the order of 0.1 mm. in a structure of the order of 1 mm. in length. Thus muscular twinkling control would show a continuous jitter in the OH front. With control at the precapillary sphincter level, the stripping amounts to deoxygenation of the capillary line through its downstream surface from the near 20% level down to the 5% level. However, in that case, considering that the high frequency duty cycle amounts to perhaps only 10% of the length and therefore only 10% of the area, i.e. the high frequency jitter by itself is only at most a '10%' ripple on the slower 1-2 minute cycles. The problem that must be solved is what element is required to provide a slow limit cycle modulation of this high frequency jitter that holds the OH front some place within bounds. Note that the surrounding tissue has sufficient 'instantaneous' oxygen and whatever makes much longer 'oxygen debt' or causes shifting in flows with activity is not to be invoked. What is proposed here is that the unstable muscle engine metabolism cycle tries to strip the capillary tube as fast as it can -- in which the capillary tube keeps the tissue concentration up at the high frequency jitter rate, and that this local diffusive stripping represents the time delay for the one-two minute cycle. When stripped, one then needs a signal to flush the line with an increased flow. The system thus tends to be an oxygen flow control system at this level rather than a blood flow system.

It then makes sense that there is a slower seven minute adjustment of the blood flow system to correct deficiencies in the distribution; or if there is a change in activity, to make instantaneous changes in the distribution system. It also makes sense that in order to allow the adjustment for activity, the stops are pulled out and the action of high speed hormones - epinephrine, norepinephrine - kicks the system impulsively into a new state. However, as the last report (1) likely indicated, if there is no other call for action, the adrenalin impulse dies out in some modest time domain, say in the tens of seconds. Of the residue, first the two minute cycle takes most of it out, then the seven minute cycle resets the circulation and wipes still more of the residue, and finally the 3 hour cycle wipes the fine residue out. It is like impulsively opening the door in the dead of winter in a warm house. The impulse itself is quite short. However, if the cold wind blows on the thermostat and all power turns on in some preferred regions, then an appreciable upsetting slug of energy has been added to the system. The various modes of the system will then decay the energy, but it will take a long time.

The adrenalin system is like a 'fail-safe' system. Slug all the systems into operation in some preferred way, such as supply the brain and heart with a peak flow, for signals in the tens of seconds range, and give the system time for slower algorithms to decide upon the resetting characteristics.

Zweifach's article (11) also casts light on another suspicion that was only half voiced. One could guess from his illustration that blood flow is determined by arteriole-venule muscle cells, the thoroughfare channel muscle cells, and the direct channel shunts. It is fairly ambiguous to have the capillaries shunt the thoroughfare channels. The capillaries appear to have much higher resistance. The simpler answer, that fits the discussion, is all that the capillaries do, by their twinkling, is to cause a duty cycle in oxygen flow, not in blood flow. As large area extensions of the thoroughfare channels, their pinching off at the entrance sphincters just varies the oxygen content

of the capillary, not the blood flow shunted by that thoroughfare cell. Thus the blood flow system and the oxygen flow system are largely independent. Remembering that the capillaries are only filled to a certain limited percentage of their total extended capacity, so that they are not doing the serious blood flow shifting, but that their deoxygenation is always going on in proportion to their total - nearly fixed - area, what must change to alter the oxygen flow is where in the capillary the slowly changing OH front lies.

Thus all the conversation has turned to the microcirculation.

It was fortunate that one of the outstanding experimentalists in the microcirculation is in Cleveland. The problem was discussed with Dr. Bloch of the Dept. of Anatomy at Western Reserve. The conclusions drawn from this meeting will be deferred.

THE CARDIOVASCULAR SYSTEM

In the previous study (1), discussion was begun on modelling how the flow pulse from the heart is transformed into a pressure wave (essentially by the R-C 'wind-kessel' model of O. Frank's) and what factors transform this pressure wave and flow pulse into a signal transmitted downstream of the source. Qualitatively, it was argued that the pulse of flow remains essentially pulse-like all through the system but with a larger and larger mean flow component, and the wave of pressure remains essentially triangular all through the system, both the pressure and flow showing a transmission time delay. Superimposed on the pulse and triangle wave is the oscillatory wave, known as the Moens-Korteweg wave due to the L-C characteristics distributed through the system by virtue of elastic walls. The system shows little damping in the early part, and the oscillations damp out further out in the system. The first immediate concern is to demonstrate that this qualitative picture withstands quantitative scrutiny. If so, then the pressure and flow arterial characteristics will all have been accounted for by passive physical mechanisms. It is then possible to go on to begin to discuss the regulation and control characteristics of the system.

Geometry-Topology of the Arterial System

The predominant character of the arterial tree is that it continues to branch. As Rushmer (8) p. 5 indicates, the net cross-sectional area throughout the arterial system, regardless of the degree of division, remains moderately constant, until the arterioles are reached. There is then a large increase in cross-sectional area in the arteriole - capillary - venule beds. The proof of the near constancy of cross-sectional area is derived from the near-constancy of mean velocity in the arterial system, say of the order of 50 cm/sec. in the large tubes, and diminishing to perhaps 20 cm/sec. in the small tubes; whereas the velocity in the capillaries may have dropped to 0.7 mm/sec., a thousand-fold less. (A recent reference, Wiedeman (12) disputes the view of a change in area from arteries to capillaries. She believes that there is a uniform change in area in the arterial tree, and that capillary dimensions are smaller than commonly accepted. However, she offers no velocity evidence).

As a geometric model of the arterial system, aortic arch - subclavian - brachial-radial arterial branch will be utilized, because the somewhat quantitative primary data on dog or man that the authors propose to model for are taken in that branch (Remington, Wood 1957 data), and there is not that much

qualitative difference in the appearance of data from the terminal abdominal - femoral -- saphenous branch (see the data in (1)).

The two sources used to characterize the geometry of the arterial system were first an anatomy source, Grant's ALTAS (13), and then McDonald's (14) comments. They were examined independently. The object was first to form an independent view of the apparent geometry, and then to check this view against what the masters have likely concluded in the past.

The arterial length to diameter ratio.- The first view formed was that, after the first branchings from the aorta, it seems that the arterial lengths between branchings are approximately proportioned to diameter.

Since any particular arterial branch runs out, terminating as it does in the arteriole - capillary 'endings', in finite length, one must choose some length summing rules, and it is true that the very small tubes are quite short. It is plausible thus to examine the variation of length and diameter. There is obviously considerable statistical variation. Nevertheless it does no violence to a geometric model to consider the variation to be described as length proportional to diameter; certainly this did not seem to be violated neither more nor less in the brachial system. Thus a preliminary characterization of a total length of 100 cm. for such a system in the human (midline to fingertips) is not unfair. Then as a rough approximation, the length to diameter ratio seems to be about 20 to 1. This means that the length of 1 cm. I.D. tubes, i.e. large arteries, are of the order of 20 cm., namely of an appreciable fraction of the entire branch run. At the other end, this means that as the tubes approach capillary size, i.e. 10 micron, their lengths can be of the order of 0.02 cm; namely of the order of tenths of mm. Such microcirculation sources as (15) and (16) would confirm the latter estimate.

On the other hand, the function of the blood supply branching throughout the tissue is to supply the tissue with oxygen. If one expected the same volume of blood per unit time (the blood flow) as being carried by the major tube in each volume, taking into account the approximate constancy of blood velocity, then oxygenated blood supplied per unit time would be proportional to Vod^2, (Vo = velocity, d = tube diameter), and the tissue volume supplied would be LWH (L = Length, W = width, H = height; note, it is assumed that this chunk of tissue is chosen in similarity fashion so that the entering blood supply leaves the region deoxygenated, and just doesn't pass through, i.e. Vod^2 is proportional to how much oxygen is used up per unit time). If the tissue chunks remain geometrically similar, independant of the subdivision, then the volume supplied is proportional to L^3.

Now it is clear that no casual sizing of tubes, anatomically, can distinguish between a law of variation of d with the first power of L and the two thirds power of L. However, as the subsequent discussion will show, it is not so much a case of choosing between the two ideas, or some intermediary as an approximation, but it can be shown that it is possible to accept both ideas. The two thirds power law will give the overall topological division rate, whereas the first power law will give the local geometric rules.

The idea is conventionally projected that the measured velocities in the arterial system remains fairly constant so that the cross-sectional area open to flow would remain fairly constant. Since one is not assured that this might be an absolute rule, it is more nearly the case that as a result of a division

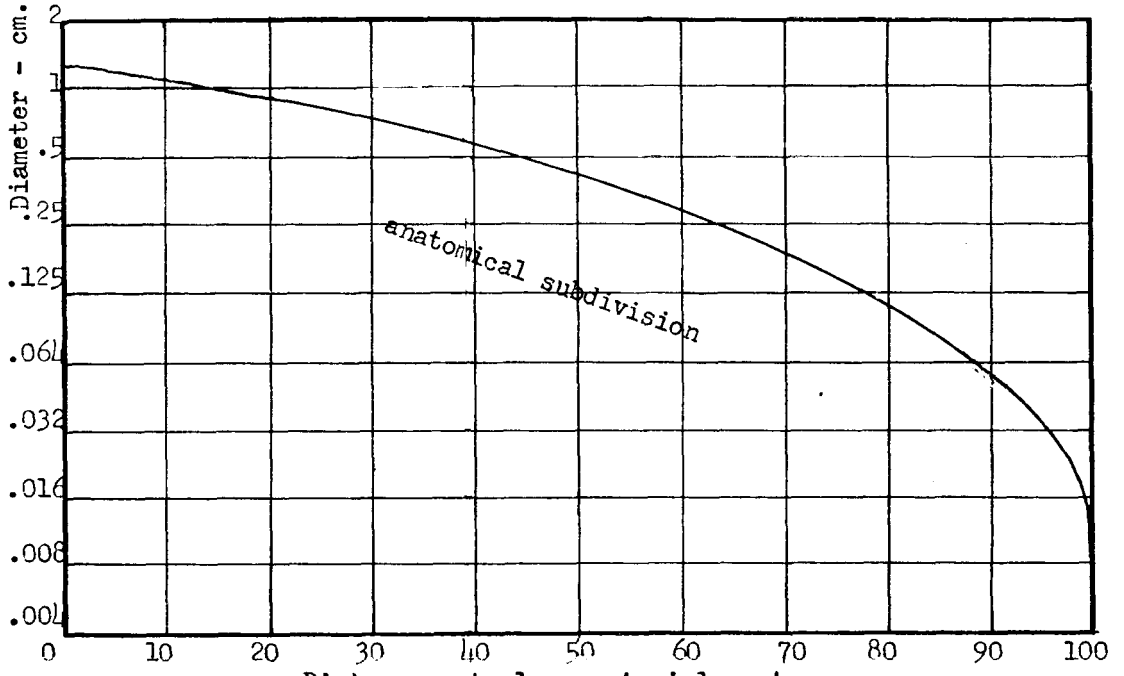
$$\frac{A_1}{A_2} = f$$

A_1 = area before the division
A_2 = area after the division
f = a 'fraction', likely less than or equal to 1.

One would estimate that f may thus be of the order of unity, but very possibly less than one, since if anything one would guess that the velocity tends to diminish further out in the system.

Branching.- While the first idea might be that there is a branching into two, the actual anatomical details indicate that it is likely different. Whether a fixed number of branchings is characteristic is not clear, but it is not impossible to decide that on the average a fixed number of branchings 'length' junction takes place.

The concept can be investigated as follows: Plot the tube diameters that one finds at various distances along the system.



Variation of Diameter along Arterial Tree-Estimated from Grant (13)

It likely appears that the concept of a uniform branching is not a perfect one. However, if a reasonable approximation is desired, mean subdivisions take place at a rate of somewhat less than but near 1.5 divisions per length.

Thus in summary a conventional view of a branching arterial system would be contained in the following table.

Conventional Arterial Tree Model
(Assuming 1.5 Branchings Per Length)

Diameter of branch	Length of branch	Cumulative distance from aorta
cm.	cm.	cm.
0.92	18	18
0.75	15	33
0.61	12	46
0.50	10	56
0.41	8	64
0.33	7	70
0.27	5	76
0.22	4	80
0.18	4	84
0.15	3	87
0.12	2	89
0.10	2	91
0.080	1.6	93
0.065	1.3	94
0.053	1.1	95
0.044	.9	96
0.036	.7	97
0.029	.6	97
0.024	.5	98
0.019	.4	98
0.016	.3	98
0.013	.2	99
0.011	.2	99
0.009	.2	99
0.007	.1	99
0.006	.1	99
0.005	.1	99
0.004	.08	99
0.003	.06	99
0.0025	.05	100
0.002	.04	-
0.0017	.03	-
0.0014	.03	
0.0011	.02	
0.0009	.02	
0.0007	.01	
0.0006	.01	
0.0005	.01	
0.0004	.01	
0.0003	.01	
0.0003	.005	
0.0002	.004	
0.0001	.002	

Whether this is a completely true picture is moot, for the following reasons: It is true that if one looks at microcirculation pictures (for example (15), which is critical of Zweifach's modeling of the microcirculation by a universal architectural structure involving 'thoroughfare' channels, of which

capillaries are side-branches), capillaries are illustrated as being of a few tenths of a mm in length; and arterioles and arteriolar channels at the 10-20-30 micron level are illustrated as being of the order of a mm in length. However, at larger diameters, it is not the case that the lengths are not interrupted by branchings. Instead, along the length, there is more extensive branchings. However, the lengths are quite extensive until the total amount of smaller branchings add up approximately to an effective equivalent equal branchings into a number M (M approximately 1.5) of branches per unit length as estimated previously.

Thus these are two possible extreme models. One, as given before, assumes that a division into M branches takes place at each counted 'node'. The other, that along each such vein, there is a distribution of smaller branches whose effective bross-sectional area per 'nodal' length equals the reduced area of the length between nodes. This latter model may be considered to be a tapered tube model. One may surmise that there is a size distribution of diameters between branches.

A basic question finally emerges as to what is it that physically determines the geometry of the cardiovascular system. The following discussion, although elementary, is extremely pertinent. One may judge from microcirculation anatomy sources (See for example the microcirculatory conferences such as (16)) that there is an extensive distribution of capillaries in tissue (As Dr. Bloch put it, any region cannot be more than 30 microns away from a blood supply). The extensive proliferation into capillaries is supplied by a much more limited number of arterioles. By examining a number of cross-sectional micrographs and drawings, it does not seem unreasonable to regard the average 'free' run of an arteriole, before it branches and along which it supplies a system of a large number of capillaries, as being about 0.2 to 1.0 mm. in length, i.e. that the arterioles can be characterized as being 0.5 ± 0.3 mm. in length and 15-30 micron or 25 ± 10 micron in diameter, and that in a square mm. of area there may be about 10 such free runs, (the count is a loose count, indicating typical numbers), or in a cubic mm. of volume that there are ten-fold or perhaps 100 such free lengths. This can be translated into the following tentative modelling hypothesis. In any volume of tissue there must be an approximately 'constant' (to an order of magnitude) number of arteriolar supply segments of approximately constant length to permit the degree of capillary proliferation that can supply the tissue. The tentative numbers of convention are chosen as 25 micron diameter, 0.5 mm. length, and 100 segments per cubic mm.

One may inquire, significantly, whether the assumed laws of artery division are adequate to account for the number of required arterioles. Patel et al (17) indicate in an average dog aorta model that there are about 30 major arteries branching off the aorta. With a human cardiac output of 4300 cc/min., and 30 tubes, there is a mean flow of about 140 cc/min. per tube. If an average velocity figure of 50 cm/sec. is adopted, then the average major arterial branch would have an area of about 0.05 $cm.^2$ or a diameter of about 0.25 cm. (The brachial artery would have a larger diameter. For large arteries, it is not unreasonable to use numbers like 0.5, 0.8, 1 cm. for diameters).

Now the degree of branching assumed, on a uniform basis, must divide tubes from 0.25 cm. by steps down to 25 microns = 0.0025 cm. or a ratio of 1 to 100. If the number of equal branches is M, and the velocities remain constant, then each division in diameter represents a reduction by $1/M^{1/2}$. If the first tube has a diameter Do, the second tube has a diameter $Do/M^{1/2}$, the third

$Do/M^{2/2}$, etc. so that the p th tube has a diameter of $Do/M^{\frac{p-1}{2}}$. If the final tube has a diameter do, then

$$\frac{Do}{do} = 100 = M^{\frac{p-1}{2}}$$

On the other hand, the number of small branches that will be produced is M^{p-1}, or with 30 major artery systems $30\ M^{p-1}$. A 150 pound man, with water density of 62 pounds per cuff has a tissue volume of about 2.5 cu. ft., or about 80 liters, or about 8×10^7 cu. mm. With 100 small tubes per cu. mm., the number of tubes required are about

$$8 \times 10^9 = 30\ M^{p-1}$$

$$3 \times 10^8 = M^{p-1}$$

or $$17{,}000 = M^{\frac{p-1}{2}}$$

One must first note that these two independent, though conceptually related estimates have been made, one of the number of subdivisions, and the second of the size of the subdivision. Both estimates have been shown to be dependant on the same parameter, M^{p-1} and thus as a first approximation, independent of the division rate. Both estimates have been shown to be of different orders of magnitude. More precisely, if that term can be used, whereas the number of small arteriole runs required is about 8×10^9, the single branching from 30 main channels would only seem to produce about $100^2 \times 30 \times 300{,}000$. It is thus quite likely that such single geometric branchings do not produce enough arterioles, although they may produce a significant number of branching lines from which much smaller tubes may arise. The conclusion that the branching topology is not by constant length to diameter ratio runs, and that a model is required in which an indeterminate large amount of smaller branching from the walls of larger tubes is required. Since a gross structure of geometric branching is already taken care of, one may regard the smaller intermediate branching to require only short runs of cms. length to be the final distributor out to the 'organs' supplied. This can be effectively simplified by only paying attention to their termini, i.e. to their last 1/2-1 mm. arteriole endings. Thus one may bring the arterioles right up to the branching arterial system, and let their number be distributed at just the uniform rate at which the tube area tapers. This may be viewed as a porous wall model of a branching arterial tree. At the present time one can say that this is likely a somewhat sophisticated elementary approximation of the system.

The major difficulty that rises to plague the problem is the threefold question of deciding on a relation between length and diameter, on the branching rate, and on the end conditions of how many large input tubes divide into how many small output tubes. What has been shown thus far is that the assumption of a linear variation between length and diameter, and any uniform branching rate cannot lead to enough subdivision to account for the number of end tubes. Therefore one answer was to add a large number of small tubes. Another answer is to change the law of variation of length to diameter, for one would intuitively feel that a subdivision into blocks could provide as many small tubes as necessary.

Illustratively, dividing an original cube by eight to preserve cubes, dividing each one by eight, etc. is one elementary process to produce a geometric similarity in the subdivision.

However, since there are other topological properties required for the blood flow subdivision such as the same continuity of each subdivision to the larger structure, one must better fit the geometric form of an elongated body - such as an arm,leg, kidney, etc. - by similarity subdivision.

For example, a typical body segment may be considered to be 100 cm. long and 6 cm. in diameter. This comes from 80 liters/30 main branches or 2700 cc. per branch. For a 100 cm. length, this amounts to 27 $cm.^2$ cross-sectional area or 6 cm. diameter. Actually one may better consider this a somewhat tapered conic pyramid.

This may be considered to be fed by a 0.25-0.5 cm. diameter artery, which itself is conically tapered.

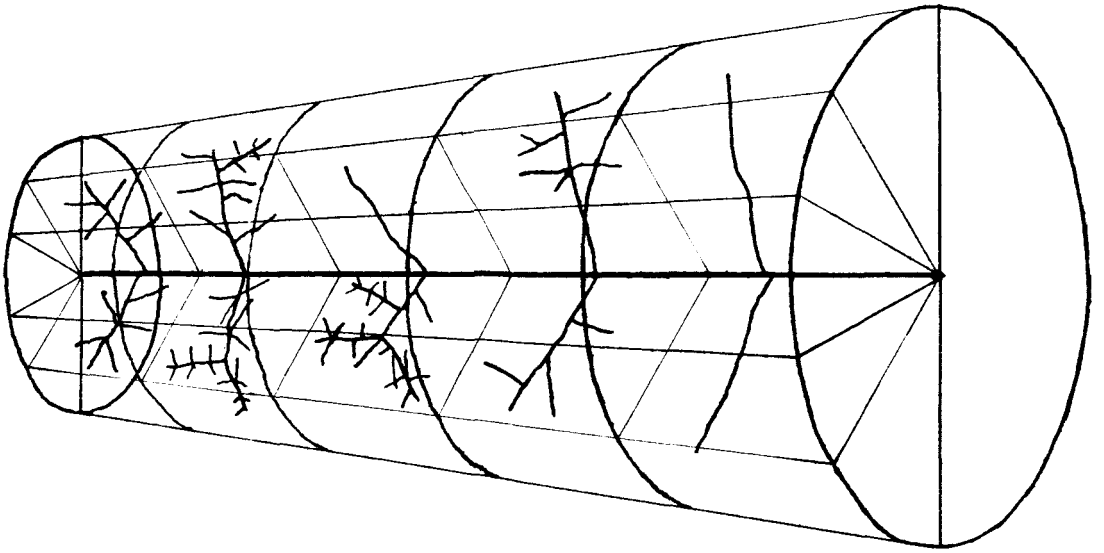
Now divide this cylindrical segment into m wedges through the axis, and slice the length n times. This produces nm segments which may be viewed when distorted as conic pyramids, in this case tapering outward. Now through each of these pyramids pass a central artery and continue the subdivision in this fashion. This will proliferate at an exceedingly rapid rate, as the following table will show.

A Topological Model for an Arterial Tree

Assumptions: Each region is supplied by same oxygenated blood supply
Each region is topologically similar
Each sub-region of tissue geometry is similar
Each sub-region is approximately a distorted conic pyramid.

	Base Diameter cm.	Length cm.	No.	Main blood tube diameter - cm.
1st division				
$D_o =$	6	$L_o = 100$	$N = 30$	$d_o = .25$
2nd division				
$D_o \left(\frac{D_o}{2L_o}\right) =$	0.20	$L_o \left(\frac{D_o}{2L_o}\right) = 3$	$2\pi\left(\frac{L_o}{D_o}\right)^3 N = 750{,}000$	$\left(\frac{D_o}{2L_o}\right)^{4/3} d_o = .025$
3rd division				
$D_o \left(\frac{D_o}{2L_o}\right)^2 =$	.006	$L_o \left(\frac{D_o}{2L_o}\right)^2 = .1$	$\pi 4\left(\frac{L_o}{D_o}\right)^6 N = 1.8 \times 10^9$	$\left(\frac{D_o}{2L_o}\right)^{4/3} d_o = .0025$

This type of topological branching is pictorially illustrated:



It is clear that the order of magnitude of arterioles in this topological model agrees with what was estimated by crude count from microscopic anatomy.

It is possible to make one further estimate of the number of arterioles for checking the topological model.

Assuming that it is true that the arteriole size dominates the resistive picture, to the point that one would most generally proceed in a hydrodynamic model by lumping all extraneous resistances into an effective moderately increased length of arteriole. The arteriole will be regarded, for conventional purposes, as being a tube 25 micron in diameter, 0.5 mm. long. If Poiseuille flow held, then

$$q = \frac{\pi d^4}{128\mu} \frac{\Delta p}{l}$$

Δp = 100 mm. Hg. = 130,000 dynes/cm^2.

d = 25 micron = 0.0025 cm.

l = 0.05 cm.

μ = 0.035 poise (assumed as a mean of data in (14)).

$$q = 7 \times 10^{-5} \quad \frac{cc}{sec.}$$

Since the velocity is given by flow per unit area, one may compute a correct mean arteriole velocity of the order of magnitude of 15 cm./sec. Since the total flow is about 4300 cc./min. = 70 cc/sec. there would have to be of the order of 10^6 effective arterioles. All of these different numbers would have to be reconciled as follows:

a. The number of arteriole runs must be of the order of 5×10^9 (0.5 mm. length)
b. The number of capillary runs must be of the order of 10^{12} (0.1 mm. length)
c. Only a few percent of the capillaries are open.

d. Therefore only a few percent of the arterioles are likely to be open.
e. A few percent of 5×10^9 arteriole tubes that are open represent a number of the order of 10^8 tubes. This number is drastically different from

(a) The 300,000 constant L/d tubes equally branching down to arteriole size.
(b) The 2×10^9 constant tissue oxygenation (constant $L/d^{2/3}$) tubes branching down to arteriole size.
(c) The $4\text{-}8 \times 10^9$ arteriole runs estimated from experimental microscopic anatomy.

On the other hand, the Zweifach-Rushmer number of 60,000 miles of capillary, taken from Krogh, would amount to perhaps 1000×10^9 capillaries of 0.1 mm. average length.

That this is reasonable is borne out as follows: If Dr. Bloch's estimate of 30 microns required separation and 0,1 mm. length is adopted, then the volume of tissue associated with a capillary is 0.003 cm. x 0.003 cm. x 0.01 cm. or 10^{-7} cm^3. On the other hand the total body volume is 70,000 cm^3. Thus the required number of such capillary runs is 10^{12}, which checks.

Such a length of capillary at say 12 micron diameter, would have a capacity of 10,000 cc., whereas the capillaries are said to only contain 5% of the blood volume of say 8 liters or 400 cc. Thus only a few percent of the capillaries are open.

(d) The only way that 10^6 effective arteriole resistances can resemble 10^8 actual open tubes is that they must be arranged in series-parallel form, namely approximately 10 series arterioles are arranged in 10 parallel branches. (While sufficient microscopic pictures have not been found, it appears reasonable that at least 4 or more series segments exist in arterioles).

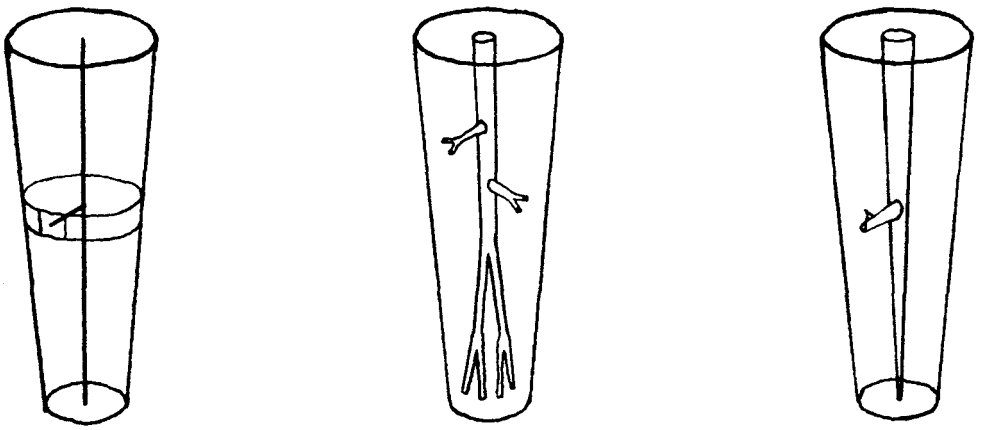
Thus one can <u>vaguely</u> begin to understand the geometric modelling of the arterial tree.

First; there is a topological branching, likely of the form proposed (i.e. the near $L/d^{2/3}$ variation of absorbing tissue length to major supplying artery diameter) of somewhat tapered cylinders. This will provide sufficient branching down to small size, the capability of uniform oxygenation of tissue, and geometric similarity from stage to stage, contiguity of all tissue segments to the major arterial supply at the level above, and a law that does not look tremendously different from complete geometric similarity (namely L/d constancy and L/D constancy). This may be considered to be a law of embryological division.

Second; there is, however, a need to satisfy geometric similarity (of a nearer constant L/d ratio). Thus the topologically determined tubes are not of constant diameter, but they reduce in size. In order that the velocity remain constant, the reduction in size is accompanied by a branching. Thus the single tube per similar geometric subdivision branches into a moderate number of major sub tubes. One thus views a stepped sequence of tubular runs along the main channel.

Third; One can follow the main channel down its length, or any size branch and find similar characteristics, but distances and time scales have changed. In particular, one can follow a main channel down, and regard it basically as a tapered tube, with a large amount of shedding into bleed tubes. The results one would get, would be expected to be not any different from writing the reflections of branches in complex form. (i.e. The system of branch to branch reflection difference equations is replaced by an equivalent continuous differential equation). It is only necessary to assume geometric properties consistent with the above model.

Modelling may thus be viewed in three steps.



The topological division model | The geometric division model | The equivalent 'physical' model

The topological model carries the gross division into similar segments; the geometric model is then the plumber's delight, in which the topological framework is eked out with a graded series of nearly constant length to diameter segments; and finally physically the whole system can be viewed as a sequence of subdivisions into tapered tubes. The ends of these tapered tubes terminate in arterioles, which consist of series-parallel branches. However, at any one instance most (namely 98%) of the arterioles are closed. Thus the resistance is most assuredly the arterioles.

MacDonald (14) has some discussion of the vascular bed, pp. 27-37. He states that changes in diameter are associated with branchings, which are then narrower; that there is a mild change in mean velocity to about 0.8 of the parent tube; that the relation of the velocity ratio of parent to branch to the square root of number of branches will determine the variation of mean pressure gradient (i.e. since the mean pressure gradient may be viewed as small, and constant or slightly increasing, this would require that the number of tubes divisions be equal to or greater than $(1/0.8)^2$ or 1.4. At a

'minimum' value of 2 divisions there would be an increase in gradient by a factor of about 1.2. These arguments just bear out again that the branching likely takes place in the range of near 1.5 to 2 branchings per run). "...The total peripheral resistance is ... dominated by the calibre of the arterioles but the other components of the vascular bed are by no means negligible," the mean arterial pressure is about 100 mm. Hg and has fallen very little in the smallest arteries in which it has been measured, about 60 mm. drop takes place in the arterioles; 15 mm. in the capillaries and venules, and about 10% in the arterial system.

Thus it still appears to remain true that the resistance lies in the arteriole bed.

A recent reference (18) on the other hand, that overlaps much of the geometric concern in the present topological - geometric modelling, lends support to the basic idea of local geometric similarity of the length to diameter ratio of arterial beds, and adds details to the architecture of branching that produces these nearly constant length to diameter 'runs' or branch lengths. At the same time it clarifies the reason why the system can also be regarded as tapering. (The system can produce a series of branch runs, i.e. lengths between branchings, that are out of balance in length to diameter ratio, by producing small side arms, but it must soon pay for it at a subsequent branching to bring the length to diameter ratio back to par).

One may summarize the system once more in a different way. It appears that embryology took care of the topological branch laws, and that growth brings the system up to near local geometric par, based on the prime law that the mean velocities throughout the system will be approximately constant. These similar relations seem to make blood systems and rivers, and may well make neural nets.

With this long, only very primitive introduction to cardiovascular geometry and topology, further physical analysis is deferred to an appendix.

An Introduction to Regulation and Control in the Cardiovascular System

Having discussed the hydrodynamic events in the arterial system, nominally, from the heart pump source through the resistive bed, in the time domain of the individual heart pulse or group of small pulses, and found that substantially all the characteristics of flow and pressure in the large arterial system are to be interpreted as the response of passive physical elements to the active pulsing pump source of flow, the problem now exists to discover and elucidate the mechanisms by which the flow pulse in that system or its derived characteristics are determined.

The system acts as a regulated or controlled system - namely at a time scale slower than the hydrodynamic scale of events in which the elements appear to be passive, there are adjustments made that change the system response by changes in one or more characteristics. It is currently regarded, for example, that two major regulators or controllers in the cardiovascular system stem from elements in the arterial system as control of resistance at the entrance to the capillaries (see (8), illustratively, p.8, 11) at the level of the arterioles. If the mean pressure is considered to drop from about 100 mm Hg in the arteries to about 10 mm Hg in the veins, roughly more than half of the drop is under the control of the arterioles. The second derives from a pressure receptor in the

carotid sinus, near the ascending arch of the aorta. There may be other receptors such as in the aorta; however, their action has not been described unequivocally. A slower hormonal control will be discussed later.

Consider first the control of resistance in the vascular bed. Discussion regarding this system was begun in the section on temperature regulation.

In elementary form, the heart pump pumps blood to a number of parallel systems. One path from the heart itself is to the pulmonary circulation. The other paths, the systemic circulations, are from the common aorta. The pulmonary circulation, a low resistance circuit supplying only alveolar membranes will be treated separately at some subsequent time. The systemic circulations each divide into the arterial pressure reservoir tree, the capillary networks, and the venous volume reservoir. The high resistance lies in the vascular bed, which in more detail consists of arterioles, capillaries, and venules.

The central arterial and venous pressures tend to remain fixed within relatively narrow ranges regardless of the total amount of blood flowing through the system (the cardiac output), the flow division among various branches, or the various levels of control and regulating action that the system can perform.

The average volume of blood in the arterial system remains fairly constant, as long as mean arterial blood pressure is fixed. On the other hand, the central venous pressure remains nearly constant although the storage on the venous side changes quite considerably.

System branching takes place to the brain, the liver, the spleen, the kidney, the G-I tract, the heart, the skeletal muscles, and the skin. The systemic circulatory resistance thus roughly consists of these eight parallel vascular beds, each with some need of independent control.

The system can be called upon to change the arterial pressure, the total flow, the heart rate, cardiac stroke volume, the flow division, the oxygen consumption. The problem is to determine the regulation and control characteristics of as many of these as are independent.

As previous discussion indicates, from (1) to the present report, the input flow pulse character, and the mean resistance setting determines the pressure wave essentially through the passive elasticity of the arterial system. Since this is not a variable under control (although it can age), this does not enter into the regulating or control cycle as a parameter. Thus for given input pulses, the pressure wave is determined by the system resistance down to the individual heart beat cycle, and more precisely down to the essential details of a high frequency 10 - 15 cps mechanical-hydrodynamic response. Thus the first concern is what can the resistance system control?

General characteristics of the microcirculation are described in Zweifach (11) and Rushmer (8). The following taken from Burton (in (5) and (8)) lists some diameters.

Dimensions - mm.

	I.D.	Wall Thickness
aorta	25	2
artery	4	1
arteriole	.03	.02
sphincter	.035	.03
capillary	.008	.001
venule	.02	.002
vein	5	.5
vena cava	30	1.5

In (11) the illustrations indicate that the thoroughfare channel may have an I.D. that is 3-5 times that of the capillary (i.e. .03 mm. compared to ,01 mm.) and that the venule bears a similar relation to the capillary (i.e. .02 mm. compared to .01 mm.), so that arteriole, venule and thoroughfare I.D. are comparable. The precapillary sphincter is shown as having a diameter similar to the capillary, so that the above table may be misleading for this control element. It would appear from photomicrographs that the precapillary sphincter operates on the 0.01 mm. opening of capillary to choke down that size.

Under these geometric circumstances, it is illusory to consider the capillaries as the flow resistance. It would appear, from Zweifach's picture, that the system consists of a series and parallel flow shunting system. Thoroughfare cells furnish a series shunt to the capillaries, and the shunt channel, which "in many tissues shunts blood directly" between arteriole and venule, furnish a parallel shunt. Muscle constrictive control is mainly of the arteriole and venule, and at the precapillary sphinter, and lesser at the thoroughfare channel and shunt channel. (The last statement is only tentative).

Since it appears as a rough approximation that there is a comparable length in capillaries and thoroughfares, one may estimate the relative flow division. By Poiseuille's law, for the same pressure drop, and the same nominal length

$$\frac{Q_1}{Q_2} = \frac{D_1^4}{D_2^4}$$

for a diameter ratio of 4 to 1, the flow ratio would be 250 to 1. Thus unless there are appreciably more than 250 capillaries shunting each thoroughfare channel, the capillaries do not govern the blood flow. Then, if in addition the number of shunt channels is an appreciable fraction of the number of thoroughfare cells, the flow control can easily reside in these two shunt systems.

Therefore, one must conclude that the capillary system is not being used for flow control, but for some other control. The two clues are contained in the following. From (11) "if all the capillaries were open at one time they would contain all of the blood of the body", and from (8) "If all the precapillary sphincters serving a capillary bed closed simultaneously, blood would not flow through these channels. However, at any one instant, some precapillary sphincterms are open and others are closed. At intervals of one-half to three minutes some sphincters close and others open."

One can guess that the capillary twinkling, likely representing neuromuscular tone in (11) "the tone of the muscle cells of the microcirculation may well be maintained by norepinephrine continuously discharged from the nerve endings, and by the level of epinephrine circulation in the blood"); and the Lewis 'intermittant' adjustments represent two time domains of the active engine cycle that the authors have sought. A high frequency '10 cps' twinkling likely represents a limit cycle oscillator involving the unstable muscle engine - oxygen flux from the capillary - adrenaline-like chemical linkage - coenzyme system that shows up as a local small oscillation in the capillary, an oscillation in the nerve system, an oscillation in the bathing chemical system, and an electrical and mechanical tonus vibration in the muscle. The lower 1-2 minute periodic frequency represents a basic throttling of the unstable engine cycle which involves the duty cycle of stripping the capillary of its oxygen. The lagging time constant may be due either to a long time diffusion rate in the tissue or a much slower governing chemical reaction rate. (Since the capillaries have been characterized as capable of high frequency response, they likely do not govern the slower response, although their total deoxygenating time might be slow. The problem is similar to the response of the eye in which the work of Stark and Young at MIT has involved distinguishing between the high frequency eye tracking adjustment, and the slower step-like saccadic adjustments).

In an even slower time domain, the resistance setting must be satisfactory to perform the vasomotor function of blood flow division among the gross eight or so flow systems - the brain, kidney, etc.

However, one must note that the function of the one-two minute cycle is to keep the muscle system in the general region of high demand -- of either output mechanical power, or heating flux — at a 'white heat' of output, by providing the region with an ample demand oxygen flux, though not necessarily or not directly blood flow. This adds another degree of freedom to the system.

Another characteristic of a separated function of blood flow and oxygen and other materials supply by the capillaries is the capillary system tends to act 'peristaltically', namely that the power elements of high differential pressure, large flux source of blood flow, and a number of muscle motor control elements permits local forcing of product without requiring a steady local flux. Thus particles, impedances, and blockages, and tearing of the local system can take place without feeding very much signal into the system. It would come as no surprise that a system making so many adjustments (at 10 cps, 1 cps, 1 cycle per 7 minutes, etc.) may not look purely fixed resistive at all time domains. Yet at the 1 cps of the heart rate, one may only infer that the local bed is still purely resistive - capacitative. Thus the best statement is that at the primary 1 cps pulsing frequency the resistive bed is pure resistive - capacitative but not passively so for longer periods. The resistance at any longer time scale is a parameter of the previous system history rather than a fixed quantity. That is why blood pressure is also a dynamic resultant.

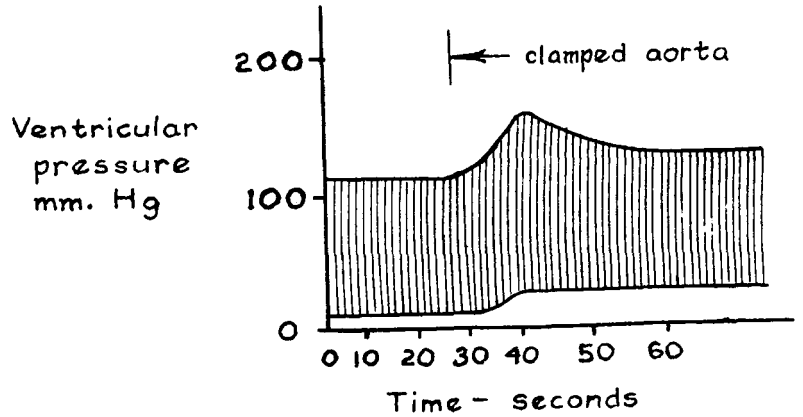
In the second report of the previous series (1), it was shown that Frank's 'windkessel' model essentially accounted for the existing blood pressure level, heartbeat to heartbeat, from the mean pressure level, the stroke volume, the ejection time, the heart rate, and the arterial elastic characteristics (The subtleties as to whether the pulse contour method can 'accurately' correlate peak pressure and flow are academic. The process in the large is so determined). One would say approximately that

pressure rise =

$$\text{arterial elastance} \times \text{stroke volume} \times \left(1 - \frac{\text{ejection time}}{\text{heart period}}\right)$$

Note that in this expression, none of the regulating or control functions show up directly. The arterial elastance is likely a near constant that only varies with age, the long time 'life' characteristics of the system, and its initial genetic characteristics.

The determinants of the stroke volume are certainly much more obscure. For example, Rushmer (8), in summary of the cardiac output, and in particular on the stroke volume states that "The quantity of blood ejected by the ventricles is represented by the difference between the volume at the end of diastolic filling and the volume at the end of systolic ejection. An increase in the diastolic distension of the ventricles produces an increase in the energy released during the subsequent systolic in accordance with Starling's law of the heart (Roughly that there is a direct proportion between the diastolic volume of the heart, as measured by its near circumferential extended muscle fiber length, and the energy set free in the following systole, which roughly measures the following stroke volume). This law was derived and confirmed by studying isolated or exposed hearts under experimental conditions in which the investigator assumed complete control. It is not as readily recognized during spontaneous activity by intact animals." The net effect of these remarks and all the discussion is that it is not clear what is the determinant of stroke, since Starling's law is simply somewhat of a statement that an increased filled volume of heart is sufficient signal to lead to an increased stroke volume, as an explanation of the stroke volume ejected by the heart. As his Fig. 10 (p. 72) indicates more nearly, if the aorta is clamped off, the entrance aorta pressure does not jump to an 'infinity', that might be expected if the heart put out a determined stroke volume, but instead the peak jumped from 110 mm Hg to 140 mm Hg in a second order overshooting reaction in which a peak of 160 mm Hg is reached in about 10 seconds and the final equilibrium in about 25 seconds. These are certainly not filling lags for the small resonant aorta volume, but are much more certainly chemical signals. On the other hand, sympathetic cardiac nerve stimulation produces a jump to 300 mm Hg., much more nearly the 'infinite' pressure that might be expected. Thus one can surmise that the stroke volume is determined by electrical signal in its operating range. The dynamics of this system are more likely then revealed by the segment of response after pinch-off.



One notes a second order response with a first time constant of the order of 3-5

seconds, and a second time constant of the order of 10-15 seconds. One may guess that the first time constant is an electro-mechanical signal in which the barostat in the carotid artery of the emptied aorta attempts to build up the restored pressure; and that the second time constant is an electro-chemical signal in which a 'counter-adrenaline' type reaction takes place to reduce the blood pressure. It is possible or likely that this second type of reaction exists at the capillary level to change the 'capillary' resistance which changes the diastolic filling but at the much slower rate.

Loosely, the nature of the performance is illustrated in Sarnoff and Mitchell (19). It is somewhat similar to the diagram in Rushmer. An increase of resistance to ventricular ejection shows a rise in aorta pressure with a single time constant judged to be about a number of seconds (in Rushmer, with a pinch-off, there was a second order damped reaction involving an overshoot and then settling back to the new higher level), and a decrease shows a similar single time constant fall.

While this paper likely opens the gateway to an extended discussion of how to discuss regulation and control of the heart from a modern point of view, it is clear that the paper is only a beginning and not a satisfactory summary of resolution of the complex interrelation between mechanical and electrical events that even the elementary reference to Rushmer suggested. Thus this problem of the carotid sinus sensor will be deferred.

Instead the thread will be picked up from the discussion with Dr. Bloch. In order to discuss variations in the resistive bed, one must begin at the level of the microcirculation. An elementary description was begun from Zweifach (11); now the conversation must get more serious.

It is clear in viewing the microcirculation (See for example (20)) that one is no longer dealing with an equilibrium hydrodynamic fluid. Instead there is a continuous interaction between gel-like particles — the red blood cells — and a streaming liquid. At the time scale of the flow events (i.e. in the tenth second and seconds domain) the tubes are essentially rigid to the pressure load, though they locally deform (and they may constrict at longer time domains). The general flow characteristics have, in recent years, begun to be attacked as a rheological problem.

As a first round of exposure, Dr. Bloch's movies were viewed, and a number of tentative conclusions made themselves evident. (Tubes were viewed in sizes from a few microns to a few hundred microns, in a variety of species, and a number of tissues both optically and by density transmission scans, at normal speed and high speed photography).

a. There is no evidence of high frequency 10 cps wall dilatation.

b. There is evidence of low frequency (i.e. in the tens of seconds or longer) contraction of capillaries and sphincters.

c. The flow patterns in the 2 - 100 micron I.D. range is about 50% loaded with cells which deform, rotate, and ooze their way through the tubes in a relatively smooth manner at the time and space scale of their forward motion.

d. <u>There is evidence of a high frequency, not irregular jitter</u>. Upon more careful investigation, by examining Dr. Bloch's sequences frame by frame, it appears that there is a moderately regular pattern of about 2-3 cps.

This jitter makes itself evident in the following manner: In high speed photographs (a few thousand frames per second) one could detect that cells were coming in groups; in TV density scanning (in about 20-30 frames per second range), one could count the density variations and note the clustering rate. In normal speed photos, at slow rates, one could also estimate the grouping rate by eye. Estimates from the different films, determined from the framing numbers, seemed to indicate the 2-3 cps rate.

Thus it appears, with a similar inversion of logic as in the aorta in which no significant longitude oscillation but only a radial oscillation was found, that in the 'capillary' vessels, the oscillations are longitudinal oscillations in cell number rather than lateral oscillations in tube diameter. However, this oscillation is the equivalent of a high frequency oscillation in the oxygen flow rate. Thus the mechanism guessed at before was wrong; even some of the proposed evidence that may have pointed to it was wrong; but the suspected hypothesis is likely right. One may estimate now that there is likely a high frequency oxygen carrier jitter in the capillary beds that furnishes the counterpart to the 10 cps in the nervous system, or the 10 cps microvibration in the muscle cells. While it is conceivable, it is not likely that these longitudinal oscillations are due to the Moens-Korteweg wave in the large arterial system.

The problem must be deferred once again, but it seems reasonably clear that the high frequency limit cycle oscillations run through all systems; that watching their action near the source, i.e. at the level of the cells whose motions can involve an inertial reaction in the limit cycle loop, shows fair indication of characteristics involving electrical phenomena, or with lesser likelihood electro-chemical phenomena, or still lesser purely chemical responses. This is only a surmise, but it is suggestive of the nature of the rheological problem that may have to be treated. It will not be possible, here, to go into any real attack on the hydrodynamics of this complex interacting rheological system. Any discussion on the possible chemical chains will be deferred at this point.

Averaging over this high frequency 'jitter', which thus means moving over to the heart beat time domain, there seems little observational evidence for any other frequency response, until near breathing rate frequencies of one per a few seconds are reached (One may not be so glib over the possible action of adrenaline-like drugs. However again this will be deferred to the hormones).

For example, a cursory discussion of so-called Traube-Hering waves from Guyton (9) p. 427, and Ruch and Fulton (21) p. 699 indicates that while these waves should be reserved for waves in blood pressure synchronous with respiration, and (21) reproduces a figure that shows a small cyclicality with respiration, there is a much more prominent 'vasomotor' wave of blood pressure in the 15-40 seconds range (Mayer wave). Guyton states that the "vasomotor waves commonly seen in almost all pressure recordings are caused mainly by oscillation of the presso-receptor reflex; a high pressure excites the pressoreceptors; this then inhibits the sympathetic nervous system and lowers the pressure." At this point, it is not clear whether the time scale covered has jumped from the response time of the baroreceptor in the carotid sinus (i.e. possible two time constant at the 3 and 10 seconds level) to the one minute frequency in capillary opening and closing. (One might note in the last report (1) a weak 25 second cycle was found in a human subject heart rate distinct from a two minute cycle). Some discussion with Dr. Matthew Levy did not resolve the difficulty, since he suggested that it is commonly regarded that pressure changes at the baroceptor site (say in an isolated preparation) will result in changes of the stroke volume, the heart rate,

and the peripheral resistance (as measured, say by the change in flow in a constant pressure perfused connected vascular system).

He supplied some data, taken with an isolated carotid sinus to which independent pulses of a number of sorts could be supplied, and with an independent vascular system (brachiocephalic) supply from a constant pressure source. From these data he proposed to indicate that heart rate, aortic pressure, aortic flow, and peripheral resistance were all changed by changes of the carotid sinus.

For example, a passing pulse (of the order of a minute) of either oxygen - low blood, or CO_2-rich blood, depressed heart rate from 120 beats/min. to 40 beats per minute. The change took place with a time step of the order of 15-20 seconds, compatible with a time constant of about 10 seconds. The rerise time seemed longer, perhaps double, but it was no longer clear whether the chemical signal was still sharp.

Thus tentatively one might consider this compatible evidence with what was mentioned before that there is a chemical signal, a chemoreceptor, if you will, in the carotid sinus, that acts with a time constant response at the 10 seconds level. This could be compatible with a second order follower characteristic seen in Rushmer's figure, or with the 25 second Weber waves. Here, note that the signal was capable of initiating very large range changes in heart rate.

Compatible with this, there seemed to be a moderate change in left ventricular pressure. Whereas, before the heart would develop a pressure pulse at a near 80 mm Hg. level, with chemical depletion and the same time constant, the pressure appeared to drop closer to 50 mm Hg.

One notes that the pressure change is not anywhere as dramatic as the rate change. This bears out what begins to be the more rational hypothesis that the pressure level is more nearly regulated by the pump than are other characteristics, and that wide shifting in other characteristics do not show much change in the pressure.

Thus, for example, the peripheral resistance changes are fairly small. In Levy's illustrations, there are ripple changes that represent levels of perhaps 5 - 10 mm Hg. at most from an 80 mm Hg. level. Levy countered that this is not a region capable of large resistance changes in the first place. The point about peripheral resistance changes is thus inconclusively resolved.

In our view, thus, chemical signal of the carotid can influence cardiovascular parameters - mainly source parameters, at the tens of seconds level; pressure signal at the carotid can influence cardiovascular parameters - mainly source parameters, at the few seconds time constant level. There seems <u>little</u> influence at these time scales on the resistive bed. The particular transforms of signal, from the carotid to the heart, whether directly, or indirectly from the central nervous system and through the sympathetic nervous system, are not being discussed at this point. Thus, for example, more rapid enervation of the heart from the sympathetic nervous system, or perhaps other sources is not being excluded. It is only the arterial sensors that seem moderately slow (i.e. seconds to tens of seconds).

In another type of excitation which Levy offered in illustration, sympathetic stimulation is done for the order of a minute. Here most prominently, one notes the formation of a near one minute cycle. Aortic pressure diminishes from

170 cc/sec. to 130 cc/sec; the brachiocephalic pressure now shows some moderate jump from 110 mm Hg to 80 mm Hg. Here it is not so clear what is happening. Electrical excitation does appear to affect heart rate, pressure, and resistance. However, it is not clear what is the nature of the coupling.

In a third type of excitation, Levy shows the effect of near one minute pulses of pressure applied mechanically to the carotid. An increase of pressure in the range 0, 100, 150, 200 mm Hg. shows little change in the 0-50-100 mm range in left ventricular pressure, but a depression with higher pressure of about 10 mm Hg. Small pips are shown in the brachiocephalic pressure. Time constants seem to be in the 3-10 second range.

The main effect of these data is to suggest that the 'baroreceptor' of the carotid sinus does not act to do any drastic control of the resistance bed, that action of the time scales of a few to tens of seconds, and directed toward heart parameters seems to be the characteristic action from this region.

Rushmer (8) references a 1958 review source by Heymans and Neil. He shows that increased pressure over about 50 mm Hg. in the carotid sinus artery puts out an increased electrical discharge frequency that varies with pressure, say in the 50 to 180 mm Hg. range. However, there are also increases in the electric discharge frequency that varies with the rate of pressure change. (However, the figure p. 150 is weak in exposing the nature of the dynamics response in electric output with any generality. For example by such statements as "if the arterial pressure rises above the normal set value, the impulse frequency increases on carotid sinus nerves, reducing the sympathetic discharge and increasing the vagal discharge. Slowing of heart rate and peripheral vasodilation restore the blood pressure to normal again." starts the discussion off as to whether such an output as electric output from a sensor here the carotid, is a unique function of level, and derivative -- here pressure level and rate -- or dependent on some slower varying property of the system -- here vaguely referred to as set point or value. This clash of ideas, which is not meant as a personal reflection on any investigator, but is nevertheless real at every point in the biological system between some physical scientists, and many biological scientists. If a correlant is to be considered deterministic, strict logic requires that its characteristic 'additive' properties be shown. The vague idea of showing responses under individual, uncombined, and non-normal operating conditions is very disturbing, and leads only to 'engineering' assumptions like that if 'all' conditions remain constant, one quantity varies as a linear combination of level and rate, i.e.

$$y = Ax + B\dot{x}$$

The issue is not to question whether this or some other result is true, but to question the proof of the underlying assumption that the system acts by such a specific correlant. One has little doubt from these and other data that electrical output arises from carotid sensors, but so what? Are the associations unique? Do they change with circumstances? What is being questioned is whether the signal is unique and really a unique effector.

The carotid sinus nerve impulses travel to medullary centers. These are returning signals, directly to the heart via the vagus nerve which appears to involve effects on the heart rate, and indirectly through the sympathetic system to the sympathetic cardiac nerve which appears to involve effects on the stroke volume, and to vasoconstrictors which change the peripheral resistance.

Of this description, it is only the peripheral changes that are in question, and of that likely only on the problem of the time scale of effect. Thus it is the interpretation of Rushmer's statements like "increase in arterial pressure increases the rate of discharge from the stretch receptors. These impulses impinge upon the medullary centers ... stimulating the vagus ... and inhibiting ... increased sympathetic discharge also enhances ... contractibility ... At the same time, the medullary "vasoconstrictor center" is inhibited, so that the total peripheral resistance is reduced. Of all ... mechanisms for changing peripheral resistance ... excitation or inhibition of the sympathetic vasoconstrictor outflow is only one which has a demonstrated role in the control of arterial pressure," that is at issue. If the adjustment of peripheral resistance is implied only at the one-two minute level or the zonal changes at the seven minute level then there is no quarrel with what the likely signals are from the carotid receptors, whether pressure or chemical.

Thus at the present, three signalling connections to the cardiovascular system have been touched on -- the control of peripheral resistance (at the two minute and seven minute level); state signalling from the carotid sinus of pressure and chemical state (exercising actions at the 3 seconds, 10 second time constant levels; possibly much lesser at the 7 minute level); and affector input signalling into the heart structure for rate, and stroke volume (at the '10' cps signalling level, 1 second rate level, and 3 seconds level. Slower regulatory adjustments also exist, but these may be mainly follower characteristics.)

This sets the stage for still a fourth control adjustment of a chemical nature. This is discussed in an article by Page et al (22) and ties into the pioneering work of Dr. Goldblatt who tried to demonstrate the connection between the kidney and high blood pressure. In the modern form of this work at the Cleveland Clinic, a chemical hormone, renin, from the kidney, produced in response to physiological 'stress', acts on a substance in the blood to form a second hormone angiotensin which acts in the arterioles to constrict them.

The experimental figures show that an injection of renin into the blood results in first order reaction rise in blood pressure from 100 to 170 mm Hg with a time constant of about 6-7 minutes. On the other hand an injection of angiotensin shows a second order reaction in which a pressure rise of about 30 mm is followed by a decay. The rise time constant is about 10-20 seconds, and the slower time constant is perhaps 5-6 minutes.

Thus it is likely that level and class of mechanisms that give rise to the seven minute vasomotor resistive shifting is here disclosed. In this one instance a chemical cycle involving blood hormones is shown. The processes are here periodic, so that the governing instability is not exposed, but as the types of data that have been explored indicate, the cyclic changes are not tremendous.

One additional factor to note carefully in the Page picture is the very prominent, but undiscussed existence of the one minute cycle. For example, it would be equally likely to discuss the angiotensin reaction as a higher than second order response, in which a 'large' oscillation at the one minute level is first invoked. (In the figure, the one minute oscillation is responsible for an initial rise of 20 mm. in the first 20 seconds. Thus the salient response very clearly noted here is aperiodic pressure changes coupled with a modulating higher frequency - 1 minute - primary cycle. It is this character of response which is gradually being uncovered as characteristic of the system. Namely, that the basic system instabilities keep a limit cycle running, and then other disturbances

-- mainly chemical -- mediate system instability to give rise to aperiodic or nearly periodic disturbances, usually first order or second order responses.

REPRISE ON THE CARDIOVASCULAR AND THERMOREGULATING SYSTEM

The discussion and review conducted in the previous two sections have finally formed a primitive view of the mechanistic system characteristics, a much weaker view of the sensor and motor characteristics, and a still weaker view of the regulation and control in the system. However, since the system is being studied like a jigsaw puzzle, it is of considerable use to repeat over and over again each subsequent view of the stage of disentanglement.

Consider the cardiovascular system and the temperature regulating system in a normal steady state of operation. (This may be at an activity level, or it may be the steady state being reached after a disturbance from some other state. It is to these final or near final steady states that attention is first addressed).

An autonomous oscillator in myocardial tissue (a completely local electrochemical oscillator of unknown nature) develops a pulsing cycle of a near 1 cps repetition rate. (The statement is so put in perhaps bad fashion because the electrical system has not been explored). This electrical signal stimulates a heart rate and a stroke volume of the heart. The stroke volume is transformed into a pressure pulse because of the arterial elasticity. At the operating condition, each second to second stroke volume determines the pulse to pulse pressure. At the existing resistive bed settings, there is sufficient resistance in a branching 'capillary' bed that a high mean pressure is sustained. The stroke to stroke volume maintains the average flow rate through the resistance. The resistance of the bed and storage capacitance of the arterial system gives rise to an 'emptying' time constant of the order of a few seconds.

Rises and falls of pressure at the time scale of a few seconds in the carotid sinus gives rise to electrical signal to the heart that modifies the heart rate and the stroke volume. Since the flow rate through the vascular bed is not particularly affected, one must judge from the Levy data that a change of a factor of three in heart rate only showed up as a change in pressure of 40%, so that a change of about a factor of two increase in stroke volume was required. No other quantitative conclusion is desired other than that signal from the carotid sinus is likely capable of making comparably large changes in heart rate and stroke volume. Because of the delay, the time scale of change is of the order of a single order time constant of about 3 seconds. However the larger sensitivity at the carotid sinus seems to be to chemical signal rather than to pressure signal. Large changes in carotid pressure (or some transform property of pressure, including differential operators) cause fairly compensating changes in heart rate and stroke volume. However, chemical disturbance of the carotid sinus (and this is much more difficult to understand, because the chemical disturbance may arise from whatever mechanism may have caused the pressure change) will cause a transient decay with a time constant of about 10 seconds. This is suggestive of (but only vague evidence for) a separate chemoreceptor, or network mechanism involving a slower diffusion time (For example the same receptor could be used, in which mechanical pressure acts directly to excite signals at the 3 seconds time delay level, whereas chemical disturbance has to diffuse at the ten seconds

level, or as in the case of the Page picture of the renin - angiotensin pair, the formation of one can involve a flow diffusion process to initiate the other).

One can only surmise that there are a series of regulatory settings of both stroke volume and heart rate that lead to essentially the correct pressure and oxygen-carbon dioxide balance of blood in the carotid sinus.

(Note that it is implied here fairly precisely, with our present limited understanding, that the adjustments that are made are purely regulatory, and thus show up in time only as transient level adjustments. Since there appears to be two constants - the 3 seconds and 10 seconds time constants — one physical, from the filling time R-C, and the other chemical, possibly a diffusion time in a local pocketed reactor such as the carotid sinus, it is not surprising — however not essential — that there be two motor mechanisms, one to adjust heart rate, and one to adjust stroke volume. There is no implication that these are absolutely independent, partially independent, or tightly coupled. We don't quite understand it at present. It is just that together an action is determined. On the other hand, it is not too surprising that these aperiodic transients can become coupled, as in the Weber wave, to produce a 25 second, i.e. 10-45 second, limit cycle instability.)

In very rough description, these two state variables are shifted as regulated settings by the variation in stroke volume and in heart rate. By virtue of associated time constants, they keep the aortic system contents adjusted in its pressure and oxygen content at the ten second level. Thus this system is nominally separated out from the regulating and control chain of the cardiovascular system.

That the oxygen content and stroke volume variations lie behind the heart is obvious. All that is being said at the moment is that electric signal goes in centrally, and comes out peripherally to offset the state of 'heart' - determined variables, in which the 'heart' is regarded as a pump source. However, now with perfect validity, the heart system has to have buried within it what we buried within it in the first place, namely the pulmonary circulation. It now makes perfect sense that there exists in the 'source', not only a capacitance to help adjust stroke volume (It is through this that Starling's law of the heart will ultimately come into perspective), but also a series-parallel oxygenating shunt system to help regulate or control the oxygenation - decarbonation of the blood. However, from the present point of view of the arterial system, these characteristics are buried as part of the dynamics of the 'heart' pump source. It was not clear at the beginning (although it may be perfectly clear to biologists) that the 'pump' connotation, dynamically, referred not only to the pump as a pressure-flow source but as a pressure-flow source of oxygen. (This concept will be perfectly comprehensible to the chemical engineer, who is accustomed to think about the near independent flow of various components).

The vascular resistance bed, in most significant respects, is essentially a slower independent system. A high frequency nervous jitter at the near 10 cps level (namely at what appeared to be a slower 2-3 cps rate) represented a flutter in the aggregation of red blood cells per unit time flowing through the resistive system. (This is not absolutely certain at this time, but is a hypothesis to provide a high frequency mechanism. It represents the remnant of the idea that was probably picked up from Krogh of a capillary twinkling and that has been detected in Dr. Bloch's pictures.) The major regulating element seems to be an opening and closing 'twinkling' of capillaries at the 1-2 minute level. This, it is proposed, is likely controlled by local tissue oxygen consumption.

Since this makes itself evident as a local limit cycle everywhere present, the source of the limit cycle instability had to be uncovered. We believe a key and central idea is that the biological muscle fiber engine is unstable and will proceed to pick up as much fuel as it can, if the reaction is not governed. It is proposed that the system uses the oxygen limiting transport for this purpose of rate governing. The limited oxygen storage of the entire system, which depends on the limited surface rate of oxygen exchange of the lungs, is what creates a field instability in which the two minute cycle shows up as a complex modality response in the whole system, i.e. the two minute cycle skims around statistically from region to region, and even appears in the input because it is also muscularly determined. The one weak element in this picture is that the mean oxidation rate, even if cycling, doesn't drift up to its peak. The nominal answer is that the system as a whole is not organized into a network of equally indifferent vascular resistance elements, but is organized into about 8 major circulations. Each major circulation is throttled by a blood flow control which determines the relative and limiting blood flow for each circulation. These circulations are organized to supply organistic system demands. The totality of such adjustment represents vasomotor activity. There is a much slower 7 minute determinant for this cycle. Since it appears both as a weak cycle as well as a stronger single time constant response, it must be a near unstable system. Its source is not known nor will it be speculated on at this point. Suffice it to say as in the aperiodic case that an organ system demand will result in a lesser throttling of blood flow to an organ. This increased flow, at the seven minute rate, will then provide a higher level of oxygen flow into that system which will then oscillate at the 1-2 minute level. Thus flow throttling of blood supply at the seven minutes level permits the 2 minute local organ cycle to fluctuate at a near saturating level of its speed of response. The blood throttling is tied by an undermined linkage to the activity level called upon in that organ by its 'muscle' fibers. The quotes represent any cells, muscle or organ, that can put a high oxygen demand on the blood flow system.

It is clear that there may be high speed dethrottling of the entire resistance system by 'hormones', i.e. such as a sudden release of adrenaline into the blood, etc. However, what is being modelled here is the slower running states of the system.

Now the problem of supplying the stomach, or the kidney, etc. or the peripheral circulation becomes a little clearer. The case of the peripheral circulation will be discussed in a little more detail.

One of the important systems circulation is the peripheral circulation for purposes of temperature control. However, as previous dialogue has indicated, the control had more than one function. For example, one may now believe, with considerable more conviction, that components from the various systemic blood supplies appear well mixed near the hypothalamus to drop off a variety of informations there either directly or by chemical correlates, or 'signals'. Specifically, one of these may be temperature. It is no surprise that an unknown algorithm of the hypothalamus shifts the systemic circulations, although perhaps only very little, at a seven minute level to adjust deep body temperature. It then no longer comes as a surprise (although it did at first) that the most common response found in Benzinger's near-hypothalamus data, particularly emphasized in his running conditions immersed in baths (discussed in (1)), was a seven minute response.

One point that had been confused before begins to clear up. It had previously been carelessly considered that the same blood flow was being used for the heat power transfer from the muscle heat engine and as heat exchanger with the outside. It is now clear that two systemic circulation systems are involved; the blood supply to the skeletal muscles, and other heat producing organs like brain, heart, G.I. tract as one system, and the peripheral circulation as the other system.

One may now view the peripheral circulation as the primary heat-transfer exchange system. At this point then the general view of the superficial circulation is of significance. As Burton states in a 1960 symposium (23) "our quantitative knowledge of the peripheral blood flow is based on plethysmographic measurements of limbs and appendages — The total blood flow, measured in this way, is the blood flow to skeletal muscle plus that to bone and that to the skin ... The general conclusion to be drawn from quantitative data is that from the point of view of its own metabolic needs, the skin is very greatly 'overperfused' with blood ... The minimum value ... in an intense vasoconstriction due to exposure to cold is of an order of magnitude (of the amount required to supply the skin tissue oxygen requirements) ... this suffices ... shown by the fact that maintenance of such intense vasoconstriction never leads to necrosis of the skin[1] ... The mean flow and the maximum skin flow are remarkably higher than this adequate minimum flow. In the skin the flow rises in vasodilation to over 100 times the minimum value, and mean values of 20 or 30 times the minimum ... The enormous range clearly indicates that the blood flow of the skin is serving the whole organism ... Examination of the variability of the blood flow of the skin shows that, in the homeothermic mammals, this is previously in the interests of the regulation of body temperature ..." By this brief excerpt, it is unequivocal in the eyes of the accepted masters, that the peripheral circulation is being used for the temperature regulation. However, it is also unequivocal that the data assembled in (1) indicates a 1-2 minute cycle in characteristics of this blood flow, consistent with data that Burton has assembled from at least as early as the mid-thirties. Thus a two minute cycle comparable to all other two minute cycles, and now pinned to the micro-circulation and likely to an unstable local 'muscle fiber' (Through an oxygen-stripping-from capillaries mechanism) must exist in the peripheral circulation. However, here this cycle has the following significant characteristic. Its temperature twinkling represents the absorption of heat from the locally heated muscle engine cycle. If the muscles are in an active state, the oxygen supply has been increased, a greater amount of heat is produced, and the blood capillaries carry the heat off. However, while they pick up the heat by their rate of change of temperature, they dump the heat by their level above environment. Thus in a relaxation oscillator follower mode, they climb up to the necessary level above ambient at which they dump. But — in the skin there are sensors. These are aware of the dumping level, and they send information centrally to reset the systemic circulation, the vasomotor response, on the seven minute level.

At this point, the concept of the so-called oxygen debt begins to have some comprehensible significance. Best and Taylor (5) p. 879, taken from Hill, illustrates basically that a change in activity level is accompanied by an oxygen consumption rate with a time constant of about 1½ minutes (This is exactly the same point from which we started in our original metabolic work). This delay time is what was basically considered by Hill to be the oxygen debt. Now it is vaguely possible to 'see' the mechanism of change. A high demand for oxygen,

[1]Our note: However Dr. Siple of the Army has called attention to the fact that in prolonged exposures, it leads to chilblains and trench foot.

say by activity level, quickly strips the particular systemic circulation or circulations involved at the near 1-2 minute time scale. This demand is a sink, and so it cannot oscillate through the system as before, but as each component of blood comes through this region, the stripping takes place. However, the vasomotor response that would reset the systemic circulations, say at this point as taking place at the hypothalamus in noting deep body temperature or oxygen content, does not take place faster than the seven minute rate. Therefore the local distribution holds up, and the follower action of changed circulation can only take place slower. The fact that there can or may be a faster hormonal action — say adrenaline — will be deferred at this time. Suffice it to say it possibly has a rapid but only limited transient action. Also the fact that there may be a second anerobic reaction at higher levels is not of concern in 'normal' operation (when Best and Taylor in particular, or other physiologists in general discuss 'anerobic' processes involving high oxygen demand, they perhaps do not make clear that they are talking about oxygen demands above 2 lpm, as compared to normal 0.3 lpm demand. As a recent study of Goldman's of Quartermaster Corps indicated for operation in the hot, or operation in the cold, or data from mountain climbing operation is concerned, it is essentially impossible to get persistent and sustained heavy exercise levels above 2 lpm oxygen consumption from humans. Short transients can lie in a range up to 3 lpm. Thus the anerobic processes are not of present concern. This is also shown in Gray's book on ventilation, that the normal range of zero to high activity level lies in the 'steady state' region which Best and Taylor describe as "in light exercise the lactic acid is removed during the work — the body 'pays as it goes' — and no oxygen debt is incurred. This is called the steady state." However, they state that "the average man cannot maintain the steady state unless the oxygen requirement does not exceed about 2 liters per minute." Coupled with the present quite authoritatively derived estimate that steady and persistent heavy work cannot maintain an oxygen consumption level of greater than 2 lpm, it leaves the clear indication that the usual steady state exercise processes do not involve the quite casual common view of many physiologists about the oxygen debt as being a disequilibrium oxygen process. It was originally thought that an 'oxygen debt' in the system was intolerable because the sytem had to run at very near chemical oxidation equilibrium in steady state operation; now it appears that rate depletion processes, not the chemical equilibrium, but the physical-chemical diffusive stripping of oxygen, has a local time domain of about 2 minutes. Thus heavy demands in one system can be met by a single systemic storage time of two minutes, but as a warning it is likely not possible to call on many of them simultaneously. Thus you cannot swim heavily and digest your food strongly, you cannot carry heavy loads and use your brain most effectively, etc. Some small degree of poetic license is contained in the last statement, though not much.

Viewed again, the two minute time constant arises from the stripping of the muscle of the oxygen in the tissue associated with its supply capillaries — the capacitance is in the blood content, and the resistance is in the path consisting of the oxyhemoglobin bond, the capillary wall, a sheath around the capillary, the tissue, a sheath around the inside unit, and the muscle unit. Which is the real resistance is not known at this point. The relaxation portion of the cycle arises from an as yet unaccounted for chemical step, say that shuts down the capillary or muscle and allows the system to recharge. (Either the muscle can shut down and the capillary recharges, or the capillary shuts down, and causes a correlary shut down in muscle. This may very well work on dynamic rate changes similar to ground water well recharging problems. This is discussed later in more detail).

Having the local heat exchange going, it is not surprising that there is an algorithm at the hypothalamus which determines whether a slower resetting takes place. Thus both the 2 minute and a seven minute cycle makes itself evident in the heat flux. Also, the seven minute cycle controls the rate at which the vasodilation or constriction takes place, as was found in the thermographs in (1). Here it was found that the blood resetting, as marked by the occurence of those regions whose surface temperature shed off to near ambient temperature, took place at the seven minutes level, as time constants, with gentle seven minutes cycles superimposed.

The reason that the term algorithm is used for the hypothalamus code book of interactions is that its scope, i.e. its serial coding, is so complicated that a 'book' is needed, of many pages, rather than a simple line of instructions. We are much too ignorant at this time to 'guess' the entire algorithm. Nevertheless it is clear that it contains Benzinger's proposal of high temperature sensitivity.

However, now a more acceptable picture begins to form of the nature of temperature control, regarding the question of surface sensing versus deep body sensing. It is hardly an overstatement to describe dialogue in this area among investigators as being lively. It appears in our terms that surface temperature sensing is involved in the control of the superficial peripheral circulation's fundamental 2 minute cycle. It appears that deep body sensing, at the vasomotor level, regulates the systemic circulations to add more or less heat circulation to the skin. It then is no longer quite so much a mystery as to how temperature pulsing continues to occur at the extremities even in the cold. The withdrawl of peripheral blood flux interposes the equivalent of a large thermal resistance over the body without changing the core circulations too much. (We had had great difficulty in fully accepting the near complete independences of the peripheral and more internal circulations).

Sweating can now also be reasonably associated with these two mechanisms. As Hertzman shows, in (16) or in earlier papers, there certainly is a near 2 minute cycle at each surface station in sweating, and he also shows, as in his Fig. 4, near 10 minute cycles in extremities flow. (In forearm say as compared with finger the cycle amplitude is much less). He showed earlier that the sweating is a cyclic response in the number of sweat glands per unit area that were twinkling. He also accepts and finds that there is a considerable degree of specificity in skin temperature, cutaneous blood flow, and sweat rate. Hertzman states that likely "sweating and cutaneous blood flow are coincidental rather than causally related phenomena". At the present time it is sufficient to describe the cutaneous capillary system as being endowed by temperature sensitive sensors which develop a twinkling of sweat glands related to the two minute capillary opening and closing cycles, and involving an increasing number of sweat glands per unit area as the skin temperature approaches 35° C. The evaporation of the sweat of course helps further to remove heat and cool the body.

Such mechanisms may appear to be casually thrown together for the function, but this is not true. It is more likely the best evidence for the existence of regulating functions, for as was stressed in (1), one does not know precisely what design criteria existed in the mind of the designer, and it is only by very careful examination of system characteristics that the approximation range of regulation can be inferred.

The body seems to have its metabolism (i.e. the supply of oxygen to the muscles and tissue at the capillary level) tied to muscular activity, and is thus

a generally regulated function with temperature changes. (It would now appear possible that the moderate rises of mean metabolism at both low and high temperature are related by the fact that one of the circulations, say the skeletal muscle circulation, is supplying a system which is doing more internal muscular work to run the blood flows needed for the heat exchanges so that it still remains true that the oxygen demand is still tied to muscular activity, here internal).

Using the detector that Benzinger has attempted to popularly expound in recent years, the hypothalamus, the systemic circulation is routed with such divisions that will maintain deep body temperature, i.e., it likely pushes out an increase or decrease in peripheral circulation. This shifting instability results in the seven minute cycle. The nature of the seven minute cycle is not uncovered. One may only note in passing that the Page et al model of blood pressure regulators involve chemical actions -- first or second order reaction systems -- at this time scale. This is not meant as demonstration of the temperature regulating cycle, but is demonstration that slow one or two step chemical reactions can take place in the circulatory system from one systemic circulation to another, to come up with long time constants, longer than blood transit time. However this general but vague model is what was postulated as possible for the two minute cycle and now this cycle, and described by the vague name of 'hormone' action.

Thus it is likely that the deep body temperature cycle of the seven minute level is regulated by the hypothalamus, and is described as vasomotor activity. It sets the zonal and surface distribution of temperature.

With the systemic 'valve' settings so determined, now the local muscle heater 'sheath', namely the skeletal muscle sheath, (which is used for rapid changing external activity) and to a lesser extent the other active organs, begin to draw oxygen into its more rapid local two minute cycle all through the body. In the peripheral circulation the local two minute twinkling, in detail, as the blood passes through the skeletal muscle sheath and in the skin, is topped off by heat exchange, and begins its external conduction out to the skin. The reaction of the skin to the temperature level at which it is operating may furnish information to the hypothalamus, as a different part of its algorithm, about the nature of skin temperature, local muscle activity (namely local shivering, which does not raise the activity level of the body as a whole, but which may be raised by local changes in the capillary twinkling to control surface oxygen flow), and at higher temperature, sweating.

All of a sudden, at this point, a physiological picture of regulation that was previously rejected is now understood. The physiological literature describes temperature regulation of the system in terms of three regions. At low temperature, metabolic regulation by raising metabolism level; at high temperature, evaporative regulation by increased sweat output; in the middle, vasomotor regulation by regulating the amount of blood to the extremities by dilatation or constriction. This modelling is not correct. However, there is a view in which it is correct. It is approximately true for the peripheral circulation component of the blood flow. Vasomotor settings determine the interior flow, and therefore what percent the peripheral circulation has to play with. By doing so, it sets the zonal limits. If these settings are wrong, then they will be changed. Now in the higher speed time domain, the peripheral circulation uses the extra oxygen flow to control whatever motor units it has for its temperature control. This means increased amplitude muscle excitation (i.e. likely the

surface control can reach down to a small extent and energize a small percentage of skeletal muscle) in the cold, or increased muscle excitation in the hot (i.e. in control of sweat glands). However, this peripheral control, likely surface temperature determined, only controls a limited amount of flow and therefore only a limited amount of the heat regulation.

This continues the line developed in the last report of (1) that proposed viewing temperature regulation first from the view of the 'core' of the system, stripped of its outermost linear temperature dropping zone, i.e. outside of the middle of the skeletal muscles. It emerges now with some more clarity that the basic system regulator of activity is the oxygen flow supply from the core, that the oxygen flow supply is used like electric signal to switch 'motor' units on and off through the 'unstable' two minute engine cycle. Now temperature sensing in the core sub-divides the oxygen flow, by the blood flow, to the systems by virtue of hypothalamus signals. The peripheral circulation, with its central nervous system connections, likely has separate entry to the nervous system and then proceeds to its temperature control functions through control of its micro-circulation, i.e. much of the heat exchange can be done beyond the 7 minute vaso-motor action, by dilation and constriction of the two minute level to control series and shunt flow paths.

As one further piece of evidence of the reality of the two minute cycle, observational comments of Zweifach's (16) p. 396 are pertinent. "Under conditions of relative rest, after the muscle preparation is allowed to become stabilized, many of the capillaries do not convey an active circulation through them, except intermittently. Different capillary areas open up briefly for period of 90-120 seconds. The cause of the periodicity ranges from closure of single precapillary sphincters to contraction of whole metaarterioles and even small arteriola branches to affect simultaneously 10-20 capillaries," or Dr. Lutz' counter comment that "we all seem to be seeing about the same things, but may be calling them by different names." That the cycles can also be tied to muscle action is clear in the following remarks of Dr. Knisely that "in resting muscle, a flow persists through the smallest cross-connections, (-of capillaries-) the preferential channels. Observations carried out for periods of several hours reveal scarcely any flow through the capillaries. When the nerve supply, or the muscle itself is stimulated two or three times, the whole muscle goes into powerful contraction, and very rapidly every capillary vessel opens up until the volume of blood seems to be greater than the volume of muscle. Upon stimulation and muscle contractions, the blood circulation stops briefly; in the postcontraction period, the hyperemic flow is reestablished. With time, the arterioles narrow down and various small vessels shut down, until almost no flow exists."

Two warnings exist in these comments. As Dr. Bloch carefully indicated, one must take careful note of the differences in structure and operation in different portions of the microcirculation (the blind men and elephant story) in seeking generalizations. The major resultant having been sought is to have at least one active engine system. This was found at least in the skeletal muscles and its circulation; likely also in the heart and brain circulations, and perhaps others. Whether it is absolutely general or not is not known, although temperature-depth surveys have suggested it is. Now microcirculation considerations can examine whether it is true through all circulations. The second, much more serious warning, is that the concept of a chemically unstable muscle system is wonderful, but it certainly neglects the electrical control on the muscle element. We recognize and note the criticism. However, the reader must also note that the general attack has been to proceed from the mechanical to the chemical to the

electrical. The electrical system, except to note that action potentials are frequency modulated to excite muscles, has not been exposed. We 'guess' that in general their action will be at the faster modulated levels, i.e. of the 10 cps fundamental, of 1 cps heart rate level, of the 2-4 second ventilation rate level, etc. Thus there should be a range of little conflict through the separation of the frequency domains.

A FURTHER NOTE ON THE NATURE OF LIVING SYSTEMS

The hypothesis that the muscles form an unstable engine cycle, suddenly provides a basis for a most provocative hypothesis.

The chemist and physicist commonly think of passive follower reactions in the form of

$$\frac{dx}{dt} = -Kx$$

x = a variable (such as a chemical concentration)
t = time
K = reaction rate

This, or in more complex form, illustrates common first order (or higher order) reactions. It is within the same mathematical scope to think of

$$\frac{dx}{dt} = +Kx$$

However, the physicist and chemist seldom think of it this way. The chemist does perhaps more in thinking of catastrophic reactions. We first thought about it for lethality processes involving the degradation of a biological species due to radiation or in living processes (24). Namely it dawned that this negative reaction rate process representation is a positive rate example of degradative processes, the so-called Gompertz relation of mortality processes. Though a mathematical curiosity, it was beginning to dawn that it was the representation of an active system process, rather than a simple passive relaxation. Finally at this point, the thought comes to life. Life itself is an active engine process. However, as we are beginning to grasp, it is an unstable process that tries to 'burn itself up'. The effect of all of the detailed equipment is to take the basically unstable engine (The opposite of the Arrhenius type reaction relation) and to throttle and choke it. Thus the system 'runs away' and degrades or 'explodes' at a finite rate.

$$\frac{dx}{dt} = +Kx$$

It is the increased number of active engines that keep adding more engines to fire the system. This is what makes the living system viable. This is what makes the living system expand into its environment, regardless of how difficult, with an 'explosive' rate constant, until some dissipative rate saturates the process and turns the result toward a more passive relaxation process i.e.

$$\frac{dx}{dt} = +K_1x - K_2x$$

K_1 = explosion rate constant from active engines

K_2 = reaction rate.

The processes are non-linear, so that these ideas are only descriptive. While philosophic, it is believed that this idea is one further key to what is necessary to unlock the biological system.

HORMONAL DYNAMICS

Preliminary Comments on the Water Oscillator

In pursuing the thread of the biological system description in a first year of effort (1), the main line chosen was that from Cannon's homeostatis to Smith's unfolding of the story of the significance of the kidney as a general regulator of many functions of body content. As the study progressed a dynamic basis was proposed for homeostasis as dynamic regulation by shifting the stability of internal oscillators, and the key thought was voiced that the system was made up of a connected sequence of loosely coupled oscillators. Water level remained a somewhat passively regulated system, although right from the first report at least Zinsser's remarks were reported on that there still remains considerable mystery in the (what at the time of writing appeared to be only the mechanism of) operation of the kidney. In the third report experimental evidence was shown for a near three day oscillator cycle in the weight content, and it was proposed that this represented a sustained non-linear limit cycle oscillator in the water level. If so, it would appear that such a cycle is hormonally mediated. Further review of the literature does not show any extensive discussion of the oscillator, although it appears reasonable that endocrinologists are familiar with weight-water changes.

The basic problem is encountered in weight regulation, where as was briefly touched on in the first report (1) there is coupling between food intakes and water changes. Thus if one is an oscillator, the other one is also. Furthermore what is being discussed is a richer harmonic spectrum than just an eating cycle, or even an elementary eating-drinking-voiding cycle, as its involvement in a three day cycle or in a longer menstrual cycle will easily indicate. In the latter two instances, the case for hormonal involvement must be strong.

Considered first, data in Best and Taylor (5) p. 867, taken from Newburg, shows a dynamic response with 1 pound cycling of about a 3 days periodicity. However, what is interesting is to note a time delay of about the order of 15 days. Actually the system data seems to be a second order system involving an integrative term, so that equilibrium in about 30 days is shown. The system is shown unbalanced by as much as 6-7 pounds. The figure clearly labels the effect as due to water retention.

Thus it is quite obvious that calorie intake by itself is <u>not</u> a unique determinant of weight. We were in no position to voice this sort of belief before, first because we didn't believe it, and second we had no way to test its truth or falsity. There was just sufficient general information around — perhaps much of a bar talk nature — that provided nagging thoughts. Furthermore along this line 'practical' clinical experience and physiological - physical experience seem at some odds with each other. Yet it is the coupling between the water and food system, both of an oscillator nature which must provide the way out to a reconciling hypothesis.

Even more striking confirmation of the 'guess' (based on data in the 3rd report that a 3 day hormonal cycle must exist, must be water dependent, and that it can easily be found in weight regimes) was found in an article by Gordon et al on weight control (25).

First, their weight responses in dieting, illustratively their Fig. 10, are almost identical in frequency and amplitude response to what was found in (1). The oscillatory amplitude is of the order of 2 - 4 pounds with a near 3 day cycle. It appears that the near 3 days cycle is characteristic of humans, although the amplitude may be individual dependent.

The 'pathological' concern of the article is not of present interest. Suffice it to say that the article offers evidence for the abnormal findings of "failure to lose weight, even when maintained for prolonged periods on severe caloric restriction", and about 26 other characteristic disturbances in many obese subjects. It is interesting to note that the major ideas that are promulgated are that "eating habits of the vast majority of obese human subjects seem almost certainly to be more than a coincidence," that the nature of the storage seems to be different, and that some encouraging success in control of obesity is obtained by rather drastic changes in eating patterns to break up the metabolic and storage pattern. Although all they state "in commenting on this regimen of therapy, it is worth emphasizing again that it contains no philosophic ideas about weight control..." on the contrary, "it is formulated, instead on measured abnormalities in the metabolic functions of obese patients in the hope of achieving a plan of therapy for weight reduction by correcting each one," the important point is that water disturbance is the only apparent plausible thought that most people can come up with in the light of the 'facts'. "It has always appeared to be a paradox of thermodynamics for any human ... to subsist for a prolonged period on a severe caloric restriction and still manifest no weight loss ... phenomenon ... is well known in the medical literature ... as is familiar experience to every clinician who has studied obese subjects ... under carefully controlled conditions ... it must have some reasonable explanation ... in all probability it is the remarkable defect in renal excretion of water that accompanies the obese state ..." Furthermore they point out that oxidation of fatty tissue produces at least as great a water yield as the weight of the tissue. They state that the problem of fluid retention in obesity is generally much more severe in female patients, that this is not likely estrogen dependent, but involves accumulation of true edema fluid. With diuretics, some female patients continue fluid retention for many weeks without weight loss, and even weight gain. Furthermore they can show marked postural differences in human subjects in renal clearance. As illustration, under fasting, steady diuresis is produced over a nine hour test period by supplying 200 cc per $\frac{1}{2}$ hr. H_2O. In the first 3 hours of test, the patient stands; in the second, he lies down; in the third, he stands. The diuresis is very marked in the second period, and low in the other two periods. Many obese patients (particularly women) note puffiness or even pitting edema of the ankles in the evening because of this postural effect.

Within the same scope of effects noted in this article (25), we happened to find a human female subject with these problems in even more exaggerated form. The subject is married to a physician, in her thirties, with 3 young children, with a near reasonable weight (120 pounds) for her height (5 foot 2 inches). Apparently on a diet similar to that recommended in (26), of not eating for two days, and then confined to 500 calories per day for the next five days (although she had been on equally confined uniform calorie diets for longer periods before) she just barely managed to hold her weight down. On any sort of near 'normal'

calorie diet, she would puff up and gain 20 pounds. Since she had been dieting on this sort of level for at least a year or two, one must note that a daily deficit of the order of 1000 calories should represent an effective loss of 2 pounds per week, or 50 pounds per six month period. One has to be prepared therefore to consider out of balances in the metabolic picture abnormally by as much as 20 pounds or more, and a more 'ordinary' unbalance of 10 pounds as illustrated in (5) as being quite usual and possible in a 'normal' range of operation of the system. One must be prepared to accept that these weight unbalances are tied to a water - food oxidation process, involving storage and burning; that there must be a related chemical linkage in the regulation and control chain; that the linkage must involve hormones; that both cyclic and aperiodic processes are involved; that both processes occur at long time domains, such as 3 - 15 days (i.e. periodic 3 days phenomena has been shown); and that this must be the near fundamental weight regulating cycle. Thus the 'fundamental' oscillator cycles of the system, are the 10 cps nervous signal; the 1 cps heart beat; the 15 cpm ventilation rate; the two minute motor unit engine cycle; now the 3 days water - food recharging cycle. (There are of course many other intermediate cycles most of which are auxiliary, but a few that have so far been missed may be fundamental).

A sharp dialogue is needed on the water system. As Newburg showed (26), if one corrects for the water balance, the loss in weight of a fasting subject could be accounted for, very nearly (i.e. to fractions of a pound) by the calorie balance. Newburgh concludes "These many painstaking investigations of the metabolism of obese persons have failed to disclose any abnormal process that accounts for the accumulation of the fat. On the contrary, they have demonstrated that obese persons produce more heat in the basal state, that they expend more energy to perform a measured amount of work, and that their total heat production is greater than that of normal persons of similar age, height and sex under the same circumstances. Since they are unable to absorb more energy from their food, they must eat more than normal people simply to avoid loss of weight."

(More modern data on the same theme is contained in a 1964 study, reported on in July to AMA Meeting in Chicago, by Kinsell and described in a science survey in the newspapers, indicated that 3 obese persons on 1200 calorie per day diets, one high in carbohydrates, one high in fat, one high in protein, all lost approximately the same weight. "Apparently 1200 calories are 1200 calories, and it doesn't make much difference what form they are in as far as losing weight is concerned.")

Thus once more the attention can be focussed on the critical question. What determines the equilibrium weight level of an individual? It is obvious that the average calorie intake is equal to the average calorie output (else, by the classic studies, there would be an ultimate weight change). One may accept with Newburgh, or the literature more generally, that calorie input level is at most a very insensitive function of weight. For example, it is likely, that a normal range of activity requires somewhat more calorie intake for an obese person than a skinny person. However, it still does not answer the question of what determined the weight level of the two. It is also clear that moderate changes in basal rate are regarded as weak evidences for differences in thyroid function (presumably dating from the studies of Magnus-Levy).

Although these and a variety of other ideas are stressed in (5), (9) and (21) what they do not stress is that water is tied up in an oscillator complex.

Consider the parallels in the two systems - food and water. Both are taken in on a number of hours periodicity. Both are excreted in small amounts, in that the system tries to take out all the possible calorie value that it can (of those molecular links that it can attack) from food, and thus excretes only a little, and it similarly fully utilizes water. Both systems have a second large output, for energy control. Food puts out mass byproducts that represent work output. Water puts itself out as a mass byproduct for heat energy control. However, they are linked in a number of ways. Chemically, the oxidation of one, food, produces water; physically, water is used to dilute the food. In the fluid stream the proportions are fairly regulated, as are their nominal average contents in the body. They both have circulations devoted to their regulation.

Where is the apparent difference? The water operates in a three day cycle. Thyroid action seems to be very weakly connected with weight, weakly related to basal heat production, but fairly strongly related to 'instantaneous' heat production, but on the basis of a five day time scale. Is there not a growing presumptive evidence that these two are related? The following is therefore proposed as a hypothesis.

The thyroid hormone is implicated in the three day water oscillator (one may profitably return again to a paper by Gerritzen at the Second Conference on Biological Rhythms, Utrecht 1939, or we have viewed our ideas against the background in (21)) whether directly or through TSH. One might surmise that the thyroid oscillator cycle determines the water oscillation. The water frequency is tied down; but the water oscillation amplitude is not as closely regulated. This water cycle amplitude is a major determinant of the food digestion cycle, and the operating calorie rate level. The individual adopts an activity level for other than physiological reasons - namely mainly psychological reasons. The body development then takes place to force a concord between the thyroid - water - calorie determined input level and the activity - weight level. If the calorie intake is high, and the body activity is low, then the body grows fat so that a higher calorie output is needed to perform that moderate activity level.

Thus weight is determined as a slowly changing dynamic resultant between a physiologically determined mean metabolic level (averaged over days) and a psychologically determined activity level. Body weight then rises and falls to determine a size at which the calorie output will be used up in both the external activity level and the internal activity level required to drag around the body that performs the external activity.

This does not violate the shorter time energy demands, which were run by a muscle engine cycle. After all dragging the body around puts the energy demand on the system now through the internal energy consuming 'muscles'. It does violence to the concept of the 'instantaneous' energy demand.

However, one must remember that most studies have shown the surprising result that week in and week out calorie levels tend to remain fairly uniform for rather active and inactive personnel in both warm and cold. Persons called on to put out work, do so, but there is a tendency in the longer run to compensate and knock the average levels down (see for example, Carlson (27)). Thus these demands are probably met by a much shorter range supply system, adrenaline, which offers an increased oxygen supply to the muscles as a rapid response to 'activity' demand. Nor is the thyroid response the determinant of basal metabolic rate, although by measuring the basal rate, you can find what level of basic internal activity level the system at its operating weight has adapted to.

The thyroid most likely must be involved in a cycle that determines the level of water content. It may do this by a sodium cycle which may then tie up the water cycle. To the extent that this is true, one can view the human as a water content, whose level is homeokinetically determined, and to which food is then proportioned to maintain the dissolved solids operating levels. If now, the external work calorie demands are inadequate, solid weight is stored as fat, with an attendant increase in external work.

If these theses are true, then it is an approximate waste of time to force 'diets' on normal but overweight people. As Drs. Page and Hellerstein (Cleveland Press, August 3, 1964) are beginning to stress, exercise is as essential to life as sleeping and eating. "Mechanization is making us a fat, lazy, indolent, bored society of people who are aging prematurely ... exercise will help you lose weight, resist disease ... fat is reduced and redistributed; blood pressure is lowered; the heart beats more slowly and gains more resting time ... the cholesterol level is reduced; fatigue is reduced ...". The issue is not whether these results are temporary fads or not (we do not believe that they are) but that the apparent paradox is shown even in these clinically based studies that greater average activity level tends toward a more satisfactory operating level of the system, of lower weights generally, and that the mechanized anti-effort resultants of industrial civilization have tended toward weight rises.

Thus putting together the results of fairly uniformly regulated calorie intakes and fairly regulated social activity patterns, one is forced to the resolution proposed here, that weight rises to the level at which the internal activity level makes up the difference between calorie intake and external work output. One may view this as being somewhat revolutionary, even if quite simple.

However, accepting this concept provisionally, forces the search for hormonal action, in particular thyroid action on to the control of the water side. It also revises our understanding of Cannon's homeostatis.

The biological system, even in higher animals, seeks a dynamic regulation of its watery interior milieu even on the input side, and not just as a regulation on the output side. In the human the water level is regulated by a thyroid based complex at the three days level. This would not be surprising in the ameba. It is now wondered whether this really is surprising in the human.

Whether this long chain involves the hypothalamus, or the hypothalamus is only involved at the hours or shorter level, is not clear. Ruch and Fulton (21) call attention to such experiments as Anderson and McCann, where electrical stimulation of the hypothalamus caused increase of up to 40% of body weight.

Thus, hypothetically, one begins to view the hormonal action (namely the action of a chemical signal that travels long distances through the blood), by what one vaguely can see as common to all of these systems. It is best illustrated possibly in the Page (22) picture.

A fundamental oscillator cycle exists. This is locally determined by some sort of mediated local instability involving a chemical link. (In the Page data it is the 1 minute cycle. In the temperature data it was the same one-two minute cycle. In other units it may be the heart beat, etc.). A 'stress' put on some organ system (namely, in physical terms, some significant change in the ambient-external or internal environment) results in a 'chemical' signal that

enters into the blood stream. Some other systemic circulation branch may produce a mean steady rate reaction chemical. The interaction of these two chemical flow streams builds up reacting components. The interaction may be mediated by a hormone signal acting as a catalyst. One component may lead to a slower more permanent one time constant step change (with some much slower decay - say as the renin change in blood pressure). The other component may circulate through the system, and, likely in the vascular bed where the products are well mixed, result in a two time constant step change, one relatively slower than the other in which both the finite chemical signal stream and its reacting by-products disappear, leaving again only the sustained oscillation. One must note that the first encounter of this sort took place in the thermoregulation studies (10) where instead of finding a difference in temperature flux and oxygen or ventilation rate at low, medium, and high temperature, only one type of sustained oscillation was found. In the third report of (1) the experiments reported on of injecting a near dozen hormones into the blood were somewhat disappointing in not producing much system effect on the ventilation rate and the heart rate oscillators (except for adrenalin and possibly acetycholine) in the time domain minutes to hours. However now it is wondered whether this isn't all the general type of direct 'power' response that one might expect. (The communications response becomes a somewhat different thing, involving power amplification rather than direct power transformation). In the case of adrenaline, it appeared that one gets a transient second order response.

From this specific case of weight variation, and its parallels to the other system we begin further dialogue on the hormonal system.

It has become generally apparent that before any valid explanations of hormone mechanisms can be arrived at, it is essential to unravel from the many apparent physiological effects and duplication of effects the primary effect and function of each individual hormone. Examples of initial successes in this direction are the trophic hormones of the pituitary whose main function is apparently stimulating the production of one or more hormones in other organs. This has led to a feedback - non linear oscillating model of the interacting systems, for example, the TSH - thyroid system and a tentative mechanism for regulating the levels of the stimulated hormone, in this case, the thyroid hormones. The postulated action of the trophic hormones is on the enzymes which catalyze the production of the target hormone or are instrumental in the growth of cells in which the target hormones are manufactured. The level of target hormone in the blood regulates, by an inverse relation, the level of trophic hormone production or elaboration into the blood.

Detailed actions are still a mystery but at least there is a reasonable suggestion where to look.

However, in the case of the other common hormones like adrenalin, thyroid, etc., the many physiologic effects -- many duplicated by other hormones -- has made it difficult to isolate a primary action, and thus difficult to know where to look for the primary action and its mechanism.

A direction, common in study of physical systems generally, for attempting to match the hormones with the primary body actions they affect, and thus helping to unravel the specific mechanism of a hormone's action is based on the temporal analysis of its normal physiological effects.

It has been considered suitable for these early studies to confine the investigation to time domains associated with the other systems being studied in this program and with hormones apparently associated with these system and with these time domains.

Body activities can be broken down according to the frequency of action. It is postulated that the correlation of action time of a hormone with the action time of a body activity may serve to indicate the primary action of the hormone. The action times of some important body activities are

10 cycles per second	-	nervous system, individual muscle fiber contraction
1 cycle per second	-	muscle organ contraction, for example heartbeat
5 seconds per cycle	-	breathing
1-2 minute per cycle	-	heat production
7 minute per cycle	-	blood flow cycles into larger systems
35 minute per cycle	-	gas exchange in body tissue
3½ hours per cycle	-	heat balance of the body as a whole
3 days per cycle	-	water (and food?) balance.

The more rapid cycles are presently presumed to be mediated electrically. The breathing cycle is presumed to be regulated by the CO_2 partial pressure in the lungs. Therefore, it appears that the slower cycles are the ones most likely to be mediated by centrally produced hormones, which then require at least the circulation time of the blood for transit from point of manufacture or storage to the site of action. If more than one step or blood-carried substance is involved, several transit times would be required for the effect to be evidenced.

Thus any of the cycles, 2 minutes or longer are of interest; though at the beginning of the program (1) the longer period hormones, sex, growth, etc., were eliminated from consideration because of the experimental difficulties inherent in dynamic studies of long duration. Since the three day cycle was independently found in this program and is apparently related to the shorter heat producing activities and the overall water balance, this cycle has been now included.

The objective in this report is to attempt to produce tentative links between particular hormones and the body action at the time domains listed above, excluding the first three higher frequency actions. (These actions are probably mediated by neurosecretions like acetylcholine but they are not hormones in the sense of being liberated at one site for an action carried on at a site, removed from the origin. It should be noted, however, that the difference between substances like acetylcholine and adrenaline, especially in relation to their biological actions, could easily end up being only academic.)

Thus five cycles remain. Of these the 3½ hour cycle is apparently dependend on ratios of body volume to body area, and is not likely to involve hormonal action. The 35 minute cycle is perhaps associated with gross O_2 - CO_2 exchanges between the tissue, the lungs, and blood. It has not been considered in connection with hormone dynamics.

Thus, a first major concern is with three major cycles, the 2 minute heat production cycle, the seven minute vasodilatation cycle, and the three day water and food balance cycle.

It is proposed to consider each cycle and the hormones which appear to be most likely involved in the operative mechanisms, separately. A discussion is also included of the blood sugar - insulin interaction. It is in the time scale, perhaps a little shorter than the 2 minute cycle, in its faster phase, although its action during absorption of ingested sugar is with an apparent much longer period. If there is a relation between the sugar - insulin action and the heat production cycle, it is not clear at this time. It was included because of the clear indication of cycles in blood sugar concentrations with considerable indication that the homeostatic regulation is achieved through these cycles.

The Two Minute Heat Production Cycle

The two minute heat production cycle is of especial interest because of its metabolic heat production involvement in temperature regulation.

It has now been postulated that this 2 minute cycle may be a result of a 2 minute cycle in oxygen flow, likely based on a 2 minute cycle in capillary blood flow, which is thus a two minute cycle in the oxygen supply. It has been further postulated that the muscles have an unlimited capacity to use all available fuel and oxygen and can only be controlled by limiting one or both of the raw materials.

Since the fuel supply available to the cells in the blood is large by comparison to the oxygen supply, the rate limiting process is likely to be based on the oxygen supply. Thus, there appears to be a two minute cycle in capillary blood flow (the capillaries opening and closing) causing a two minute cycle in oxygen flow to the local tissue, which produces a two minute cycle overall in heat production.

That the basic muscle action is one of an unstable oxygen - limited engine is further evidenced in a preliminary fashion by the effects of high oxygen concentrations and pressures on muscles in animals noted earlier. Representative is an article by Marshall and Lambertsen (28). They report that "Oxygen at greater than 3 atm. pressure precipitated convulsions in the mice in the absence of carbon dioxide. These convulsions were sometimes preceded by extensive cleaning of the face and genitalia; however, this same activity was often seen during the period of increasing pressure and was probably non-specific. Following this, but still preceding the seizure, a period of tremor and apparent ataxia was frequently seen that seemed to become more prominent with elevation of the p CO_2. The actual seizures were of the clonicotonic type lasting from 5 to 15 seconds; the postical period persisted for a like period of time."

It is thus suggestive that an increasing oxygen supply can cause the muscles to contract at ever increasing rates until convulsive seizures and death result. However, more systematic evidence is required before such a direct relation can be considered to have been conclusively shown.

It would be necessary to demonstrate that the external oxygen pressures were being reflected by higher oxygen partial pressures in the blood (which is probably true); that the metabolism and oxygen consumption rose accordingly (this is suggested by the extensive activity noted); that the body temperature rose, if there was no compensating heat dissipation; and that there was no other specific toxic action of high oxygen pressures to account for the physiological changes. Nevertheless, such experiments are suggestive that oxygen supply is a choke.

It seems that adrenalin is the hormone most likely to mediate this cycle. The following outlines the chain of reasoning which has led to this conclusion.

a. The two minute cycle is a major heat production cycle.

b. Capillaries open and close in a 2 minute cycle. Thus the blood supply and the oxygen supply to cells is provided in a two minute cycle.

c. Adrenalin in small concentrations is a vasodilator with a time period of about two minutes.

d. The vasodilatation effect is produced in muscles (and not in skin) where the main heat production has been postulated to take place.

e. A major action of adrenalin is calorigenic, i.e. it produces an increase in metabolism. It is thus likely to be involved in a heat production cycle.

f. Adrenalin (as does high pressure oxygen) produces muscle tremors; and skeletal muscle activity and heat production have already been related.

Some of these lines of evidence will be discussed in detail.

That adrenalin has a vasodilator action has been shown conclusively in Barcroft & Swan (29). They state that Grant and Pearson in 1938 ... "found that the intravenous injection of small doses of adrenalin caused a great increase in the calf blood flow ... Allen, Barcroft and Edholm (1946) investigated the problem in some detail and confirmed Holling's finding (1939), observing a large transient dilatation in the forearm (which) did not last longer than two minutes after which the flow subsided to about double its initial value."

Other conclusions of this work were that the transient vasodilatation is due to the direct action of adrenaline on the vessels of the limb, that the transient vasodilatation occurred in the muscles and not in the skin (the skin pales), and that the transient vasodilation "was clearly not dependent upon the presence of the vasomotor nerves." The transient vasodilatation reaches a peak of three to four fold in about 20 to 30 seconds and decays to the sustained level of double the original flow in about another minute. The total time of the transient action is about two minutes, which thus checks the time of the two minute heat production cycle.

It is possible that adrenalin action is to relax the sphincter muscles at the entrance to the arterioles and capillaries, thereby permitting the capillaries to open and allow the passage of arteriole blood. This opening and closing of the capillaries in a two minute cycle monitors an oxygen supply cycle and results in a heat production cycle from the muscle cells all with the same period. As subsequent discussion will indicate, it is likely possible that adrenalin is capable of affecting capillary opening.

Further evidence of the adrenalin mediation on the heat production cycle is indicated in the fact that the vasodilatation action is apparently concentrated in the muscle, where it has been postulated most of the heat production takes place in a subshivering level of intermittent muscle fiber discharges (tone). The skin circulation is apparently specifically excluded from adrenalin action; thus adrenalin acts on the heat production but other mediators are involved in

the mechanics for control of circulation in the skin either by vasodilation leading to sweating and increased evaporative heat loss or vasoconstriction and a higher insulating effect.

Further evidence that adrenalin is implicated comes from its well known calorigenic action.

A summary of the work to 1951 is given by Griffith (30). According to the author "Boothby and Sandiford in 1922, following as they say a suggestion of Lusk, introduced the term 'calorigenic action' to describe the increase in the respiratory metabolism of animals and man which is caused by administration of adrenaline and to distinguish this response from any type of specific dynamic action, and especially that of carbohydrate which was at first thought by them to be the basis of the adrenaline effect." The article reviews the evidence for "respiratory metabolism of the organism as a whole" and concludes that "negative results are due to some special and unsuspected experimental condition and do not represent what may be considered the normal typical direct effect of adrenaline on total respiratory metabolism." A list of experiments is then presented which "demonstrate an increase of total respiratory metabolism for the organism as a whole following the administration of adrenaline."

The author notes that "although a conclusion in such a matter cannot be decided merely by majority vote, this overwhelming preponderance of affirmative evidence would seem to leave little doubt that the characteristic effect of adrenaline on the organism as a whole is stimulation of metabolic rate. And if this would need further substantiation, there is a large body of evidence regarding its effect on body temperature pointing in the same direction; as does also the effect of a number of related adrenaline-like or sympathomimetic compounds for both of which there is no space for documentation here.

"Increase of the metabolic rate of the organism as a whole by adrenaline may then be accepted as an established fact; an explanation of how this increase is brought about is, however, still not agreed upon."

The article then inquires into the possibility that "adrenaline acts directly on the cell to stimulate the respiratory metabolism." Boothby and Sandiford are again referred to as "finding that the increase of metabolic rate by adrenaline in the dosages they used and in the unanesthesized dog is large while blood sugar elevation is slight as compared with the small increase in metabolic rate and high elevation of blood sugar produced by glucose injection. They thus concluded that adrenaline is a direct cellular respiratory catalyst" ... and calculated "that 50 calories are produced per milligram of adrenaline or 9150 calories per milligram-mol." Issekutz et al (1943) and Joyet-Lavergne (1945) are cited as agreeing with this concept.

However, the author then cites many experiments in which "adrenaline may decrease the metabolic rate of cells and tissues" under certain conditions. For example, "leg oxygen consumption is decreased together with blood flow following intra-arterial injection in the cat (Griffith and Humel, 1930, is cited); in the perfused dog leg oxygen consumption is decreased by concentrations over $10^{-8.5}$ which are vasoconstrictors (Authors note: Euler, 1931, 1932, is cited; the fact that higher concentrations, presumably above physiologic levels, produce vasoconstriction and lower metabolism doesn't really argue against the proposed physiologic action at low concentrations); oxygen usage by the contracting gastrocnemius of the cat and dog is usually decreased but it depends on blood flow" (Ginetsinskii et al, 1930 are cited).

Another series of references are cited that "...adrenaline may have no effect on cell or tissue respiration." One reference is to "leg oxygen consumption is not changed ... in the cat leg in situ except as may be explained by the change of blood flow following intravenous or intra-arterial administration (Griffith et al, 1940; Griffith et al, 1939; total of 5 references, are cited)."

Then there are references that "adrenaline may increase cell and tissue respiration." Most of this work is with heart muscle. Thus, one reference is to "an increase of respiratory metabolism but it is only in proportion to the extra activity in the isolated perfused heart (Gauer & Kramer, 1939; Rohde, 1912, 1913; Unger, 1914)."

The author then points out that apparently low concentrations stimulate the action and high concentrations inhibit the action, noting that this concentration effect has "been reported for blood cells, frog muscle brei, the perfused leg, and to the suppression of calorigenic action for the entire animal, which it is asserted occurs under anesthesis (Tsuhamoto, 1929; Radsma, 1941; Euler, 1932; Klein and Weiss, 1928)."

The author concludes that "the evidence that adrenaline causes the beating heart to use more oxygen then would be demanded by the mere work done looks fairly conclusive, but it is not without contradiction. The evidence from perfused organs or body parts such as a leg is most of it not conclusive because the increases or decreases of oxygen consumption are complicated by concommitant changes in flow rate of blood or perfusion fluid..." "My own conclusion is that the case for adrenaline being a direct stimulant (or depressant) of cellular respiration has not been proven, much as one may regret having to come to such a conclusion in regard to so simple and attractive a theory..."

The possibility is then discussed that "adrenaline increases carbohydrate utilization in the body and that this is the basis of the increase in respiratory metabolism." It is noted that such action could be again on a cellular level, or due to the hyperglycemic action, or perhaps to alteration of the permeability of the cells for glucose. "To this finally is added a variant of the usual carbohydrate metabolism theory based on the formation of lactic acid and its reconversion to glycogen."

Again, there are many references that "adrenaline decreases carbohydrate metabolism"; many references that "adrenaline has no effect on carbohydrate metabolism"; and still more references that "adrenaline increases carbohydrate metabolism." On the two questions of whether the action is due to the hyperglycemia and whether there is any cell permeability to carbohydrate effect, Griffith says the evidence indicates the answer is no for both.

Since adrenaline does cause an increase in blood lactic acid, it has been suggested by the Coris that the reconversion of the lactic acid to glycogen is the mechanism of calorigenic action by way of carbohydrate metabolism. On the other hand no relation has been clearly shown between metabolic rate and elevation of blood lactic acid. This could mean that it is the lactic acid metabolism within the cell which is important, and it isn't reflected in the blood lactic acid.

Since it appears that the lactic acid rise in blood is tied to the circulation, it is concluded that direct reference to effects on circulation might help to clarify the picture.

The effect on circulation is considered in relation to altered cardiac activity, peripheral vasoconstriction, and internal vasoconstriction. The conclusion is reached that the vasoconstriction effects are important in the calorigenic action whereas the altered cardiac activity is not.

The next point discussed is that of "tissue and organ blood flow and respiratory metabolism." It is concluded that "There would appear then to be good reason to believe that the effect of adrenaline on blood flow may have a marked effect on oxygen consumption and until there is more proof than exists at present, it would seem unnecessary to invoke an additional direct effect on cellular respiration, especially in view of the contradictory nature of the evidence..."

Plasma skimming is invoked to explain the difference in glucose uptake, unhindered and oxygen consumption, hindered, in similar vasoconstriction conditions. This plasma skimming was first noted by Krogh (Authors' note. Interpreted by us as accompanied by a high frequency jitter in the red blood cell flow), and "later emphasized by Hartman et al (1928, 1929)". It refers to an apparent separation of blood cells from plasma so that whereas the plasma may enter the capillaries and provide glucose for uptake by cells, the blood cells do not enter the capillaries and thus effectively limit the oxygen available to the cells. This evidently occurs in vasoconstriction, and presumably with large adrenaline dosages — unphysiologic doses.

On the subject of adrenaline and skeletal muscle activity, it is noted that "adrenaline produces tremors which are ascribed to direct action on the heat regulating center (Doblin, 1912; Doblin and Fleischmann, 1913); there are twitching and increased excitability of muscle in situ ... (Bornstein, 1927); in decapitated cats, normal and eviscerated, there frequently develops a hypersensitive state so that during adrenaline intravenous infusion, there is constant muscular fibrillation all over the body ... (Choi, 1928); as observed microscopically, adrenaline causes fine and extremely rapid vibration and twitching of skeletal muscle fibers (Hartman et al, 1928, 1929); tremors following adrenaline originate peripherally since they are not associated with any disturbance of orientation of the hand (Linde and Norlin, 1930); skeletal muscle and not the viscere determines all variations of total metabolic rate (Matakos, 1931) ... tremors of unanesthesized rats following subcutaneous injection of 0.02 mg of adrenaline per 100 gm of body weight prevent determination of true basal values for the first hour after injection (Bunnell and Griffith, 1939)."

"In spite of some contradictions, particularly of interpretation, most of these testify to an increase in the development of tension by skeletal muscle as a consequence of adrenaline action; and more could be cited as to its stimulation of restlessness and overt bodily movement which need not be given here since the calorigenic action seems to have been tacitly assumed by nearly all to be an augmentation of the 'basal' rate of 'resting' cells. But with lactic acid formation increased both by adrenaline and the responses involved in normal stimulation and development of tension, it is impossible not to wonder just how the adrenaline effect is to be differentiated from a direct stimulation of muscular contraction or where the calorigenic response stops and the fine rapid microscopic vibration of Hartman or the obvious tremors and twitchings of others begin. Or, finally, is the calorigenic response merely the metabolism of muscle tone and graded contraction under another name? If so, then it would follow as reported by Boothby and Vidlicka (1924), and Rapport (1929) that calorigenic energy, as usually regarded, cannot be used in muscle work and the two are only additive; as of course would be a very little and perhaps microscopically unnoticeable development of tension and an additional amount sufficient to do work."

It is likely that much of the confusion reflected in this review of work before 1950 is a result of (1) lack of differentiation between vasoconstriction and vasodilatation caused by different dose levels of adrenaline though this is mentioned and discussed; (2) lack of clear separation between effects on muscle and effects on other tissue; and (3) the serious disturbances produces by some of the drastic experimental procedures. Thus the work cited above in Barcroft and Swan and below in Lundholm is clarifying on these points.

The key points from this review as related to the major thesis that adrenaline is mediating the two minute heat production cycle are that:

a. Adrenaline raises the metabolism of the organism as a whole;
b. It is likely doing this by increasing discharges of skeletal muscle up to and including production of tremors;
c. It is likely effecting the calorigenic action by a vasodilatation effect;
d. It does not apparently produce the effect on metabolism by entering directly into the respiratory action at the cellular level;
e. Though adrenaline causes altered cardiac activity, this does not appear to be directly involved in the calorigenic effect.

Their further remarks on heat production in muscles were considered interesting in foreshadowing the findings and conclusions in (10) based on temperature and metabolism measurements, and essentially physical attempts at descriptions of the systems involved.

Lundholm in a more recent article (31) states that adrenaline in low concentration produces vasodilatation in skeletal muscle vessels while in high concentrations it produces a vasoconstriction effect.

The vasodilating effect is due to lactic acid production which is induced by adrenaline in skeletal muscle and in the heart. This lactic acid action is indicated by the fact that alkalization which converts lactic acid to lactate, weakens the dilator effect.

Adrenalin causes a rise in systolic pressure and a fall in diastolic pressure. The mean pressure remains constant and the cardiac output is greatly increased (up to 100%). Apparently, the primary action is to reduce peripheral resistance.

The constrictor action (presumably at higher concentrations) is a direct effect on the smooth muscle layer of skeletal muscle vessels.

It appears that the initial adrenaline effect is in the seconds range, after administration; the disappearance of adrenaline is in the thirty seconds range. (In the dog, noradrenaline produces the same effect.)

Lundholm suggests that adrenaline produced in a central source is dilute and thus produces the vasodilating effect; whereas adrenaline injected locally from a nerve ending may be vasoconstricting because it acts locally in high concentration. Thus, comparison must be made between threshold concentrations for producing lactic acid and thresholds for affecting smooth muscle directly.

On the other hand, no relation is found between blood flow and lactic acid production. With adrenaline, the blood flow returns to its initial rate in 10 to 15 minutes, even though the lactic acid continues to rise.

A rise in CO_2 production also occurs (which one would certainly expect from the increased metabolism). This is explained as due to the higher lactic acid concentration liberating CO_2 from bicarbonate in the tissues. Thus, it is suggested that there is a correlation between CO_2 and blood flow rather than of O_2 and blood flow, and the effect of adrenaline is to stimulate production of CO_2 which causes an increase in blood flow.

Lactic acid leaves the cells by diffusion since there is a concentration gradient evidenced by a mean content of 41 mg percent in muscle and 29 mg percent in the venous blood leaving the muscle.

Under basal conditions, there is an equilibrium between the lactic acid produced and the amount leaving the cells by diffusion into the blood. With adrenaline, the lactic acid production goes up 2 to 3 fold. The diffusion is slow so the lactic acid and the acidity rises in tissues.

Thus the following chain of events is suggested to account for the equilibrium. As the pH is lowered, carbon dioxide is liberated leading to vasodilatation and elevation of blood flow. Increased blood flow increases the lactic acid diffusion and CO_2 elimination. The pH rises, vasodilation and blood flow are reduced, leading to an increase in lactic acid and a repetition of the cycle. (With suitable time lags for each separate reaction, diffusion, etc., a suitable period for the cycle could be modelled. It would still be necessary to show how a constant source of adrenaline affects the period; how increased adrenaline increases the flow by increasing the rate of formation of lactic acid. An attempt at a model is made later.)

Continuing, Lundholm states, "In this way there will be interaction between those factors which tend to decrease and those which tend to increase the vasodilatation leading to a new state of equilibrium in which the amount of lactic acid produced in the cells and that diffused from the cells will again be alike ...In my experiments the new state of equilibrium that gradually appeared was distinctly reflected in the progressive diminution of the blood flow."

Thus, the blood flow returned to its initial level after 15 minutes infusion of adrenaline. During the experiment, the diffusion gradient rises by 84%. The lactic acid elimination is up 98% though the pH of the extra cellular fluid is unaffected because of the presence of K^+ which converts the lactic acid to lactate. (This is a likely explanation of the sustained vasodilatation mentioned in Barcroft & Swan to be discussed later).

According to this picture, the initial rise in blood flow is due to the initial rise in lactic acid in the tissues which takes time to come to equilibrium with the amount leaving the tissue by diffusion. Increased blood flow by more rapidly removing diffused lactic acid and thus dropping the concentration further, on the low concentration side, causes an increase in the diffusion out of the tissue.

Thus, Lundholm attempts a model of the vasodilatation action of adrenaline in skeletal muscle tied to metabolism. (An attempt will be made to build on this model.) Ultimately, he is suggesting a demand type regulator in which metabolism and thus fuel and oxygen needs determines the flow. This is not the same as having the oxygen supply controlled by the vasodilatation, to determine the metabolism.

Contrary to Lundholm's views are those by Hilton (32). In glands, a kin-informing enzyme produced by cellular activity in the glands is liberated into the blood where plasma kinin is formed, which causes local vasodilatation. In skeletal muscles there is no "evidence for release of kinin-forming enzyme following muscular contraction. Indeed, the problem of functional vasodilatation in skeletal muscle is as much of a mystery today as it was 80 years ago when Gaskell first proposed that the vasodilatation resulted from some product of muscle activity."

Among candidates for the role, textbooks mention CO_2 and lactic acid but this author disagrees because bicarbonate and lactate ion have no vasodilatation action worth mentioning. The small action, if any, is due to pH. Hydrogen ions directly were shown by Krogh not to give a large enough reaction. This appears to be in contradiction of Lundholm, but it may not be since lactic acid in the tissue could stay relatively low even if blood lactic acid is higher because of exogenous lactic acid administration.

Another factor which has been suggested is lack of oxygen but again Hilton doesn't believe there is any evidence, and though acetylcholine is a potent vasodilator, there is no evidence it is involved. In fact "stimulation of the motor nerve, which would still lead to the usual release of acetylcholine as a transmitter substance at the neuromuscular junction, had no vasodilator effect in the muscle, whereas tetanic contraction elicited by direct electrical stimulation led to the usual functional vasodilatation (Hilton, 1953)."

Histamine has also been proposed but there is no evidence it is released by active muscle and besides antihistamines have no inhibiting effect.

While note must be taken of such dissents, in our view this confuses the clarity of modelling that one is led to by Lundholm.

The transient action of adrenaline is rapid, reaching a maximum in 20-30 seconds. This is in the time order of circulation time of the blood, though perhaps a little slower. There may thus be at most a lag time of 10 to 20 seconds in the time of action of adrenaline after it reaches the muscle cell.

It is possible that the increased heart rate produced by adrenaline is also a result of the same type of action that appears to mediate the heat production. It follows from the fundamental hypothesis suggested above in connection with the muscle action in the thermoregulation section, (that limitation on the extent of action of muscles is achieved by a control of the quantity of oxygen reaching the muscle cells via the capillaries) that increased action can be attained by increasing the flow of oxygen to the muscle cells.

Now, if the adrenaline increases the overall opening of capillaries in a muscle, it will increase the frequency of discharge of the muscle fibers because of increased oxygen supply. The exact chain is probably more complex since it could involve a self stimulation of a closed loop involving heart muscle alone or it could involve the pacemaker. Most probably, an increased muscle rate in the heart works back to trigger the pacemaker in a faster cycle.

The increased blood sugar produced by adrenaline administration could be similarly the result of increased blood flow through the liver since it has been shown that a major adrenaline vasodilatation action does take place in this organ. If the ratio of liver flow to other flows goes up, the blood sugar would also go up if blood sugar is somehow proportioned to blood flow through the liver.

Barcroft & Swan (29) note that the transient vasodilatation action of adrenaline - in the two minute time scale - is followed by a sustained action at about twice the pre-adrenaline level. It is postulated by them that this action is due to another as yet unidentified humoral agent. It appears to last about 20 minutes (see their Fig. 3). It is interesting that a 20 - 30 minute cycle was previously found in metabolism and skin temperatures. Possibly similar mechanisms and agents are operative in the sustained vasodilatation action and the other actions. (Lundholm's lactic acid - vasodilatation cycle, lagged by the lactic acid diffusion from tissues to blood, provides one possible mechanisms for the sustained action. It is this lag in lactic acid diffusion, which leads to a lag in CO_2 rather than CO_2 tissue storage directly, that accounts for the 20 - 35 minute long cycle.) It is possible, that the observations of Axelrod (33) may suggest an alternate explanation (to Lundholm, above) for the sustained vasodilatation effect (i.e. for a longer 20 - 35 minute cycle). He states "after the intravenous injection of H^3 epinephrine to man, only a few percent of the catecholamine was excreted unchanged, indicating that it undergoes extensive metabolic change...The tissue distribution of H^3 epinephrine and H^3 norepinephrine was examined two minutes after a rapid intravenous injection of hormones. At this time, the H^3 catecholamines were found to be selectively localized in heart, spleen, and adrenal gland, in amounts several times the plasma level. Large amount of H^3 epinephrine were also found in the pituitary gland. H^3 norepinephrine levels in various organs and in plasma were about three times higher than those of H^3 epinephrine. Two minutes after the administration of epinephrine, most of the hormone was O-methylated to metanephrine, while less O-methylation occurred after norepinephrine. Most organ tissues retained considerable amounts of H^3 catecholamines long after the physiologic effects of the hormone disappeared. Two hours after the end of the injection, the heart and spleen contained more H^3 -norepinephrine than at two minutes. The persistence of the catecholamines in tissues is presumably due to binding which protects them from enzyme destruction. Norepinephrine appears to be bound to a greater extent than epinephrine.

"Both catecholamines were removed from the plasma and whole animal in two phases. The catecholamines disappeared rapidly in the first few minutes, followed by a more gradual fall. The first phase represents enzymic destruction, mostly by O-methylation and binding; the second, slow release from binding sites and subsequent metabolism".

Thus, an explanation of the sustained action may be the slow release of raised levels of adrenaline from binding sites.

The actual mechanism of action of adrenaline at the muscle sites is likely to be electrical rather than chemical. The rapidity of the action suggests that the adrenaline does not enter into a chemical cycle involving oxidation reactions with enzymes or other chemical reactions since even if the reactions themselves are rapid, there are delays expected due to diffusion into cells, across membranes, out of the blood, etc. It is much more likely that such rapid actions take place by changing the electrical properties of a fluid around a cell or adjacent to a membrane or even more likely the fluid medium at a nervous system synapse or at a nerve-muscle junction, thereby inhibiting or facilitating the passage of an electric nerve signal.

This may explain the rapid rise in the adrenaline actions of vasodilatations and heart rate. The more gradual though still rapid decay side of the action curve may be due to the removal of adrenaline from the blood by absorp-

tion and metabolism. These two opposing actions could account for the second order reaction process.

A possible action of adrenaline at the smooth muscle site may be one of electrical effects at the muscle cell membrane which results in relaxation of the smooth muscle and thus opening of the vessel. This is shown in Brunstock et al (34). They state:

"The excitability of visceral smooth muscle is modified by a variety of agents, e.g. transmitter substances, stretch, and hormones."

"In general, those agents which depolarize the membrane lead to increased excitability, an increased frequency of spike discharge, and hence to contraction. Some agents, however, may cause such a large depolarization that the membrane potential is reduced beyond the zone of firing and then relaxation occurs. Those agents which polarize the membrane lead to a reduced excitability, a decrease or cessation of spike discharge, and hence to relaxation."

On the action of specific agents, it is noted that "acetylcholine increases the excitability of smooth muscle and usually causes contraction either by enhancing spontaneity or by initiation of activity. The effects are always accompanied by depolarization of the smooth muscle membrane.

"The rate of depolarization produced by equiactive concentration of acetylcholine, histamine, and 5-hydroxytryptamine, in terms of the amplitude of contraction, is fastest for ACh, slower for histamine, and slower still for 5-HT (Bülbring & Burnstock, 1960). Furthermore, with a 100-fold increase in concentration, the average rate of depolarization caused by ACh is increased 4 times, whereas the rate of depolarization caused by histamine is only increased by 1.5 times.

"The stimulating action of ACh can be reversed in relaxation under a variety of conditions, e.g., in the presence of high K (Cantoni and Eastman, 1946; Graham, 1951; Rand, (1957), of eserine (Bülbring, 1954), and of high ACh (Burn and Vane (1949)).

"It is postulated by Burnstock (1958) that ACh (and probably other stimulating drugs) act on smooth muscle by simultaneously increasing the permeability to Na, K, and probably to other free ions present in the same way that ACh has been shown to act at the skeletal motor and plate (Castillo and Katz, 1954)."

On adrenaline, it is noted that

"The action of adrenaline varies considerably from preparation to preparation and from animal to animal (Bozler, 1940; Bülbring, 1960). Furthermore, its action may be reversed under a variety of conditions. For example, in fetal guinea pigs the ileum is contracted by adrenaline, in adults it is relaxed (Munro, 1933). Adrenaline relaxes a rat uterus, contracts that rabbit or human (Balassa, 1940), while in cats adrenaline relaxes the estrozen-dominated non-pregnant uterus, but contracts the pregnant uterus (Morison, 1940).

"In those preparations where adrenaline causes relaxation and loss of tone, this effect is associated with hyperpolarization of the smooth muscle membrane and reduction or cessation of spike activity.

"In those preparations where adrenaline causes contraction there is a depolarization of the membrane accompanied by increase or initiation of spike activity.

"During adrenaline relaxation the longitudinal intestinal muscle and taenia coli become inexcitable and conduction of an action potential is not possible (Bozler, 1940)."

Mechanisms of adrenaline action have been suggested, based on stimulation of sodium or potassium pumping into or out of muscle cells. Bülbring (1960), has postulated (noted in (34)) "that every observed response of smooth muscle to adrenaline should be regarded as the result of two opposing actions: depolarization due to the production of a 'passive' increase in membrane permeability, polarization due to the stimulation of an 'active' process."

It is thus possible that an adrenaline mechanism is electrical, leading to inhibition of muscle discharge and tension which could cause vasodilatation, though it certainly hasn't been shown that this <u>is</u> the action. It would be interesting to get action potentials at the sphincter muscles of capillaries and arterioles and note the effects of the disturbances caused by added physiologic level doses of adrenaline. If the two minute cycle is a vasodilatation cycle effected by sphincter muscle opening and closing arterioles and capillaries, the cycle should be detectable in the electrical response to the corresponding muscle actions.

On the other hand, inspection of microcirculation movies indicates that plasma skimming is involved in the effective oxygen flow by electrical means, definitely in the high frequency, and perhaps in the slower two minute cycle. The blood cell flow jitters at a few cycles per second in the arterial microcirculation. Thus, with the capillaries open to blood flow, the plasma skimming of Krogh provides plasma continually but blood cells only intermittently as though the individual cells were being summoned into the capillaries rather than being pushed in by blood pressure. This "summoning" is likely electrical, and possibly oscillatory by changes in polarity of the capillary walls. If this is a mechanism for flow of blood cells through capillaries at the high frequency, it is possible that a superimposed slower frequency might use these electrical effects in modulating the slower blood cell flow and thereby regulating the oxygen supply, as an augmentation of the mechanical action of opening and closing the arterioles and capillaries by action of appropriate sphincter muscles.

However, since vasodilatation in Barcroft and Swan has actually consisted of increased volume flow into the area, caused by adrenaline, the mechanical action on muscles affecting the flow of whole blood is the more reasonable explanation, unless the flow of cells is the primary resultant and increased total flow into the area is a secondary resultant of it. It must also be noted that vasodilatation by adrenaline is not dependent on a vasomotor nerve connection (29), and thus the electrical mechanism must be a depolarization of muscle cells directly.

Thus a general correlation between adrenaline and a two minute heat production cycle has been drawn on the basis of related times and the suggested actions of adrenaline. Lundholm has suggested a chain of events which could lead to a cyclic process in this time domain. Lundholm's process, involving an adrenaline effect on metabolism to produce lactic acid and CO_2 which would cause vasodilatation, and thus increased rates of removal of lactic acid, does lead to a cyclic process with the level of adrenaline a determinant of the amplitude of vasodila-

tation cycle. Lundholm's mechanism suggests that metabolism and metabolism products determine the oxygen flow through regulation of vasodilatation. The mechanism is attractive because a constant level of adrenaline regulates the mean vasodilatation and oxygen supply by its effect on a local chemical oscillator cycle in the muscle cells. As far as times of action are concerned, the adrenaline cycle of about two minutes for exogenous adrenaline could be independent of the heat production cycle (except if an increased vasodilatation takes two minutes to wash away the excess adrenaline just as apparently it takes two minutes to wash away higher concentrations of lactic acid). If Lundholm's mechanism is correct, one would expect added lactic acid or CO_2 or changes in pH to produce increased vasodilatation. The fact that they don't may be because the circulating blood has mechanisms for neutralizing their presence in a faster time scale than that of the circulation time which is required to carry the added chemicals to the target sites in or near the sphincter muscles of the arterioles and capillaries. This neutralizing effect could be accomplished by the buffers in the blood which would convert CO_2 to bicarbonate and lactic acid to lactate instantaneously.

It isn't necessary to invoke, for the adrenaline action, an effect on an enzyme in the cell. The adrenaline could still act on the cell membrane causing changes in polarity which result in muscle discharge. This action would be expected to be very rapid. The muscle discharge would produce lactic acid rapidly so that the time delay to two minutes would be the diffusion time of lactic acid out of the cell where it could act on the bicarbonate in the blood to produce CO_2. It is likely also necessary that the discharges from several cells are required to bring the CO_2 in a capillary up to the level which would cause the capillary to open.

The chain of events could thus be as follows: an open capillary fills with fresh blood which has a low CO_2 concentration. The capillary closes (on the arterial side) when the arterial blood has replaced the high CO_2 blood. The arterial blood has also brought along adrenaline to trigger the muscle discharges. With the capillary closed, the muscle cells feeding from the capillary begin to (or perhaps continue to) discharge in the high frequency cycle (the number of muscles which discharge depends on the amount of adrenaline available to the muscle cells) building up lactic acid and CO_2 in the tissues and in the closed capillary. When the CO_2 reaches a threshold level, the capillary opens and arterial blood moves in, replacing the CO_2 rich blood and the capillary closes to repeat the cycle. This cycle can be locally determined at a particular period, depending on the lag times of diffusion of lactic acid, the other reactions being presumably more rapid. Then the level of adrenaline would effect the magnitude of number of cells opening and closing but not the frequency too much. An alternative mechanism for the adrenaline and two minute cycle interaction may be that adrenaline level itself oscillates in the blood in a 2 minute cycle. This might follow from Axelrod (33), who found that injected adrenaline disappears from the blood in less than two minutes, either because of metabolism or absorption to binding sites. Thus Lundholm's basic cycle could be mediated by lactic acid cycles mediated in turn by the adrenaline cycles in the blood. This mechanism would have a two minute adrenaline supply cycle determining the operation of a faster local lactic acid vasodilatation limit cycle. No conclusion on which is the more likely time determinant is attempted at this time.

In exercise, when the response is rapid, the initial increased muscle discharge rate is probably nervous. The CO_2 production rate goes up rapidly, increasing the frequency of the capillary opening and closing cycle. This calls

forth more adrenaline from the adrenal gland, initially probably also by nervous signal but finally the balance must be reached between adrenaline demand and adrenaline liberation into the blood stream, probably by a response to a metabolic product in the blood. Thus the preoccupation as indicated in Hilton (32), and in Hyman et al (35) with the agent responsible for the hyperemic response.

Though not at present known to be connected to this two minute cycle, insulin effect on blood sugar concentrations takes place in this time domain or somewhat shorter. It is discussed now for this reason and for some similarities in the two overall regulating processes. Thus, adrenaline is apparently involved in maintenance of a requisite oxygen supply (to individual capillaries) and insulin is apparently involved in maintenance of a requisite sugar level more generally throughout the blood stream.

An important reference is the article by Anderson et al (36). They state: "The postabsorptive blood glucose level is practically never static for longer than a few moments at a time. It is a constantly changing phenomenon with sharp diphasic oscillations, each to-and-fro oscillation taking approximately 30 seconds more or less for its completion". (In the previous report in this program a 25 second cycle was demonstrated in heart rate in a human subject. It has also been discussed in the section above on the cardiovascular system that there is a chemoreceptor mechanism for blood pressure regulation which is operative in a 10 seconds time domain. The connection, if any, between the two actions isn't clear.)

"When these venous glucose readings are plotted at two minute intervals, they assume the form of smooth aperiodic undulations with wave lengths of from two to seven minutes. Repeated breakdown of these undulations at random into their component fluctuations (readings at 15 second intervals) shows each undulation to be made up of a succession of these two phased oscillations. It is proposed that the sharp venous descent in each completed oscillation represents the momentary transfer of glucose across cellular or molecular barriers. Each precipitous descent is immediately followed by an equally sharp rebound in venous glucose, a finding which can reasonably be interpreted only as resurgence of glucose back into the venous channels from behind the barriers. The speed of the rebound (when compared with the overall circulation time) would preclude there being any central origin for this precipitous rise in venous glucose".

"During postabsorption (at rest), the mean glucose level of all arterial undulations and oscillations tends to equal rather precisely that of fluctuations on the venous side. There is however, a gradual descent of this mean level over the hours of postabsorption, the difference probably representing the net captivity of glucose by the tissues in phosphorylative esterification, the overall deficit between the transfer across barriers and the venous resurgence of glucose.

"The reciprocal relationship found to exist between arterial and venous glucose levels, with the maintenance of almost identical mean values for each, further suggests that the oscillatory activity characteristic of the post-absorptive periods is one means by which the body maintains blood glucose homeostatically constant between its production by the liver and its transfer across cellular or molecular spatial barriers."

It is thus clear that the normal blood glucose oscillates in a fast cycle of perhaps 30 seconds. This time would be more validly established if the read-

ings were taken at faster rates than 15 seconds to eliminate noise at the level of interest. In any case, we may tentatively accept a high frequency cycle at about 30 seconds and indications of slower cycles of two to seven minutes. Again, there is verification of the two and seven minute cycles first noted in metabolism and skin temperatures, and then in heart rate and in the adrenaline vasodilatation effect above. It is not really surprising to find the major fuel (sugar) oscillating in a cycle similar to the basic engine cycle utilizing that fuel.

One might ask if the mediator of the two minute heat production cycle might not be the supply of sugar rather than the supply of oxygen. However, as explained previously, it is more reasonable that the oxygen supply is the determinant, since the sugar supply is maintained at a high level by a blood sugar concentration which varies only slightly in passage through the capillaries from the arterial to the venous side. In fact, just enough amplitude oscillation is maintained above a high base level to be sufficient for regulatory purposes. (Similar to the pressure in the arteries above a fairly high base pressure). The oxygen, on the other hand, is very substantially removed from the blood in the passage through the capillaries.

The observation of Anderson et al regarding "oscillatory activity ... one means by which the body maintains blood glucose homeostatically constant ..." is certainly wholeheartedly endorsed, and the concept fits in perfectly with the other dynamic regulations noted in this program and in (2)). Now recognizing that homeostatis is achieved by dynamic regulation through these oscillatory processes (engine cycles) it is necessary to determine the specific dynamics of the processes and the methods by which they are used for regulation. Anderson et al further state:

"The phenomenon of insulin action in the periphery is far more rapid than has generally been appreciated. In vivo, the transfer of glucose across peripheral barriers takes place rather massively within a matter of seconds of time after the exposure of the peripheral tissues to insulin. The total effect of insulin in this respect would seem to be registered as the summation of brief spurts of the hormone rather than the single precipitous dumping out into the blood stream of a reservoir content of the hormone. The overall glucose-lowering effect of the hormone is, accordingly, under normal conditions not linear between two widely separated points of time, but is reflected as the ultimate mean of a constantly fluctuating blood glucose level. The same aperiodic principle applies to A-V difference in respect to the tissue 'utilization of glucose'."

On "the effect of extrinsic insulin on fluctuations" the authors state:

"A very small dose of glucagon free insulin administered by vein from without shatters the spontaneous homeostatic smoothness of the normal to-and-fro venous tide of glucose both in man and in the dog. The effect of such unnatural intrusion of insulin from without is the prompt creation of 'forced oscillations' with increased amplitude of swing in both directions". (However, only one large cycle is shown in their Fig. 10 before the cycles return to slightly larger in amplitude than before the injection). "When the dose of insulin is further increased so as to become massive, the normal bidirectional flow of glucose gives way to a steady unidirectional tide of glucose across the barriers with immediate captivation. There occurs a deficiency of glucose on the side of the blood stream, with ultimate insulin reaction and reactive adrenal medullary over correction.

"The pulsatile character of the oscillations, moreover would also suggest that insulin function during the post absorptive period is never normally a linear effect on blood glucose between two points of time but is always a fluctuant phenomenon. A linear descent in glucose between two substantially spaced points of time, when it does occur, represents an unphysiologic state such as is induced by the intrusion into the picture of an unphysiologic dose of insulin from without."

It thus appears that insulin has a direct effect on the 30 second cycle, first to immediately produce the sharp increase in amplitude for one cycle with immediate return to close to normal but with increased amplitude over pre-insulin administration to produce a shift downward in the mean glucose level modulated by the two minute and then the seven minute cycles.

The similarity to the adrenaline vasodilatation effect is striking. There is a fast transient high amplitude effect followed by a quick return to a sustained level lower than the pre-insulin level. One is tempted to suggest a similar process is operative in both cases. Certainly the initial action has just enough lag to suggest that the lag is due to transit time of the hormone in the blood circulation and that the action is instantaneous once the hormone arrives at the action site, either at the muscles or at the liver. This causes the rapid drop in blood sugar.

The rapid recovery rise in blood sugar is not as easily explained by a second opposing action which removes the insulin metabolically since it is still necessary to explain where the sugar comes from. Anderson et al propose that the insulin action is to effectively open the barriers to sugar passage equally in and out of the cells so that there is a resurgence of sugar back into the blood from the cells and presumably from the liver. The gradual shift downward in the mean blood sugar is a result of an increased sugar passage. This implies a limited capacity on the part of the cell for capture. Then the question arises how does the very large dose of insulin produce the 'unphysiologic' unidirectional drop in blood sugar without resurgence. Also, what is the mechanism for resurgence in the normal resting state and is insulin the regulator of that cycle?

The other important question to be explained is the action during the absorptive stage. A second order process is indicated in the usual glucose tolerance tests. The blood sugar administered intravenously rises to a maximum in 4 minutes and decays to the normal mean in 30 to 40 minutes. When administered orally, the rise time is longer, presumably a function of digestion time and absorption into the blood. With the rise in blood sugar, a second reaction is started which acts to remove the sugar by storage in the liver and presumably in the other cells of the body. The removal to storage is reputedly mediated by insulin. However, since it occurs at a slower time rate than that of normal insulin action, it is likely that still another hormone is involved.

It is possible that two hormones are at work, one effecting rise in blood sugar presumably by liberation from storage in the liver and the other effecting removal from the blood to storage in the liver and other body cells. However, as Anderson et al point out this cycle (is the resting state) occurs in thirty seconds, and the circulation time is not much shorter, so that there wouldn't be time to complete the necessary number of blood circulation cycles - for the change from rising blood sugar, to hormone (insulin from the pancreas), to dropping blood sugar, to hormone which causes blood sugar rise, to blood sugar rise,

and back to insulin. This adds up to four circulation times which even at 10-20 seconds per cycle would require a minute or more for completion.

One could postulate a single site and a single hormone with decay effected by rapid removal of the hormone by metabolism or binding with inactivation as evidently occurs with adrenaline. The most likely site would be the storage at the liver. Now, a rising blood sugar triggers an insulin release which circulates to the liver in about 15 seconds, and promotes the storage, thus dropping the blood sugar. The insulin is absorbed or metabolized and disappears in a 15 second period, permitting the sugar release to start again. A thirty second cycle could perhaps be squeezed into these two circulation times, but the fit looks tight. On the other hand a thirty second rise and fall time occurring primarily at the liver would generate waves of similar periodicity throughout the blood stream with changes at the liver reflected throughout the system. The comment by Anderson et al that there isn't enough time for circulation from a central control source would not be valid if the entire blood sugar concentration wave was being generated at a central source and being transmitted as a wave throughout the system. The wave might be out of phase with the source but the overall time necessary for each cycle would be the same as at the source. This is similar to the transmission of a pressure pulse in the arterial system. In fact it is likely that the analogy is even closer than expected. It is likely that the liver produces a blood sugar concentration pulse that is transmitted along the arteries to the capillaries. Removal at the capillaries is then uniform just as the capillary blood flow results in uniform removal of blood from the arterial system.

Now we have further analogy to the blood flow system in that the capillary opening and closing cycle, which at the two and seven minute cycles serves as a secondary slower resistance regulation of blood pressure, is similarly reflected in regulation of blood sugar at the slower level by influencing the removal at the capillaries.

The rapidity of insulin action, apparently only delayed by transit time through the circulation, suggests that it, like adrenaline must act not by chemical or physical mechanisms involving diffusion delays, etc., but rather by electrical effects on the fluids around membranes or at nerve-cell interfaces. Cell permeability effects, if they can operate by changes in polarity or some similar very rapid mechanisms are thus valid postulates of the hormone action.

It is still necessary to postulate a reasonable action at the liver. In the resting postabsorption state, blood sugar concentrations rise and fall in a thirty second cycle - mediated by the hormone insulin which acts to increase permeability and absorption by cells including liver cells of sugar. In the absence of insulin, the liver will liberate sugar freely. The insulin is formed in the pancreas and is liberated into the blood when the blood sugar is rising. The liberated insulin travels to the liver in 15 seconds, and, by increasing the absorption of sugar from the blood, causes the blood sugar to start down. This looks like it would take too long. However, if there is coupling between the liver and the pancreas, the sugar concentration wave reaches the pancreas as a wave and produces an insulin wave back to the liver which is in approximately the right phase to produce a sugar absorption wave which results in the corresponding sugar concentration wave in the blood.

To complete the picture it is necessary that there be a mechanism for the rapid immobilization of insulin at the liver either by absorption, binding, or metabolism.

It is now no longer necessary to call upon resurgence to explain the rise in blood sugar after the steep drop resulting from administration of exogenous insulin. As soon as the insulin disappears from the blood the liver starts putting out sugar again and the blood sugar rises. The wave in concentration seen at a vein in an extremity was formed at the liver in a 30 second cycle and has simply taken an extra 15 seconds to reach the extremity. This explanation is reinforced by the fact that the curve in Anderson et al shows a 15 second delay after administration of insulin before the blood sugar starts dropping. This is the one circulation time period that is required for the insulin to get to the liver and for the lowered blood sugar to return to a vein where it is sampled.

In the light of the general oscillators ideas proposed in this scale, it is possible that an autonomous oscillator mechanism acts at the liver to produce the blood sugar concentration wave. This oscillator is then affected by the insulin, possibly produced and expelled into the blood through another autonomous oscillator mechanism at the pancreas. This kind of mechanism fits in better with the overall oscillators interactions idea but there is no evidence for it at present in this case though it is suggested by Anderson's idea of a resurgence of sugar from the cells back into the blood. Then, the blood sugar transfer across a membrane is likely itself to be an active transfer effected by an engine cycle. (It is certainly reasonable that the active transport of other substances like sodium ions which occurs against concentration gradients is also effected by engine cycles). Perhaps, in subsequent work, it may be possible to uncover evidence for such engine cycles since such evidence is being actively and deliberately sought as the key to the operation of all of the biological systems.

The sugar-insulin interaction is thus seen to be a more rapid one than that of adrenaline in its most common effects of vasodilatation and increasing the heart rate. It is therefore possible that the effect of adrenaline on blood sugar-causing it to rise in contrast to the insulin action - is a secondary effect, perhaps, a vasodilatation action in the liver which increased flow and results in a new dynamic equilibrium with higher mean blood sugar flows from the liver.

It is not clear at this time why similar pairs of chemicals appear to be liberated jointly into the blood stream for several hormone producing organs, such as adrenaline and noradrenaline (epinephrin and norepinephrin), vasopressin and oxytocin, and insulin and glucagon. The actions of the individuals of a pair are generally different in quality and quantity of effect, sometimes exactly opposite like insulin and glucagon. One may certainly expect that such pairs could act as push-pull springs to achieve homeostatic regulation. This was suggested by Cannon in pairs like adrenaline and insulin for blood sugar regulation. It is still an attractive hypotheses but there appears not to be sufficient evidence to back it up. It will require careful determination of the dynamics of the individual actions of hormones and their effects to determine whether the hormone-pair is the mechanism of homeostatic regulation.

The Seven Minute Blood Flow Cycle

It has been postulated that this seven minute cycle involves the oscillating slow shifting of blood circulations in and out of large body areas and organs. It has been further postulated that this movement is under direct control of the hypothalamus. The suggestive observations for this are the following:

a. From Benzinger's data (see discussion in (1)) on correlations of hypothalamus temperature with ambient and skin temperature, it appears the major cycle in hypothalamus temperature is a seven minute cycle, contrary to the finding in ventilation rate and skin temperature in which the two minute cycle is the most prominent.

b. From experiments in the cold temperature oscillations near the extremities, where the skin temperature passes into an unregulated zone and begins to approach ambient, demonstrate the seven minute time scale most prominently. Since it is this zone which is under vasoconstrictive regulation, it is suggestive that the seven minute cycle is involved in such changes of blood flow to appreciable size areas.

c. The period of warm-up required to bring a large muscle area to maximum efficiency is of the order of seven minutes, indicating that whatever actions stimulate the maximum blood flow to provide greatest possible supply of oxygen and fuel to a particular area, they must adapt via seven minute cycle normally acting in the blood flow.

d. The relaxation to normal after activity similarly takes about 5 to 10 minutes, again indicating the high amplitudes can decay only within the 7 minute blood flow cycle.

It is thus of interest as to what is a likely mechanism by which the hypothalamus achieves a seven minute regulation of blood flow to an area. Since a large area is generally involved, a first hypothetical suggestion might be that one nervous system to each particular modest sized arterial bed system would be sufficient to regulate the flow to the entire area supplied. Thus the hypothalamus could shift blood flows from one major organ to another by a system of nervous connections. However, it has been shown that the major resistance to flow is in the arterioles and capillaries. Thus to achieve changes in the resistance, it is always necessary to act at these size levels of passageways. Now, if the regulation were purely nervous, separate nerves would be required to each of the small vessels. It is therefore more reasonable to expect that such regulation would more likely take place via a chemical signal which might act in conjunction with one or a few major nervous signaling systems to the entire area.

As in the case of adrenaline and the two minute cycle, it is likely that the normal resting seven minute cycle is mediated by a particular concentration level of a hormone in the blood. Raising the concentration level in the blood has the effect of raising the amplitude of flow into an entire area by affecting more capillaries or arterioles within the period of each seven minute cycle. A particular mechanism is not clear at present, but the following tentative speculations are made.

a. Since the hypothalamus is involved, it is likely that the hormone comes from the pituitary and probably from the neurohypophysis, which appears most directly linked to the hypothalamus anatomically.

b. The hormones liberated from this area, vasopressin and oxytocin, especially the former, have been shown to have effects on water flow, especially through the kidney and thus appear to have the right kind of action.

c. The time of action of vasopressin, the anti diuretic hormone is rapid and its half life in the body is of the order of 8 minutes. Thus, the time of action is the right order of magnitude.

Thus as a first very tentative hypothesis, it is proposed that vasopressin is the hormone responsible for the seven minute blood flow cycle. It is not clear whether its primary action is on the kidney - in a seven minute diuretic - anti diuretic effect with this cycle only reflected in the rest of the blood flow because of the relatively large percentage going through kidney (25%) or if the primary action in the normal state is on all the microcirculation of the body equally, with the flow effect producing an antidiuretic effect in the kidney.

This would suggest further that the seven minute cycle is not produced by effecting the vasodilatation side but rather the vasoconstricting side, considering that the major action of vasopressin is antidiuretic and vasoconstrictive. This ties in then with the fact that vasopressin is a mild vasopressor presumably a result of increasing the resistance in the arteriole and capillary beds.

This appears to contradict the accepted view of vasopressin diuretic action as being due to facilitation of reabsorption of water in the distal tubules in the kidney. Such a mechanism would not account for the vasopressor action except it be due to oscillations in the blood volume, which would also be reflected in oscillation in blood flow.

On second thought, a mechanism of specific action in the kidney to account for the entire blood flow cycle throughout the body leaves the warm-up periods and the relaxation time after activity, not quite satisfyingly explained. It would be more reasonable to have an all pervasive seven minute cycle regulating larger blood flow patterns with a specific resultant of this action occurring in the kidney.

An early proposal that extract from the pituitary affects capillaries and arterioles came from Krogh (37) who found that commercial pituitrin contracts these vessels leaving the veins unaffected. After summarizing the evidence on other possible hormonal and chemical effectors, Krogh concludes that it is probably a pituitary factor which is responsible for capillary tonus. He disagrees with Dale and Richards who suggested that adrenaline in very low concentrations were responsible for maintaining capillary tonus. He notes that a large histamine dose produces low blood pressure with greater accumulation of blood in capillaries of viscera and little accumulation in the skeletal muscles (this thus also eliminates histamine as a mediator in the 2 minute heat production cycle).

The time scale of action of vasopressin is indicated for example in Thomas (38). He measured the effect of vasopressin on urine flow and some urine constituents, and found that a rise in the urinary creatinine concentration and urine to plasma creatinine concentration ratio occurred within 3 - 5½ minutes, and a drop in the urinary osmolality/creatinine and urea/creatinine concentration ratios occurred in the first or second collection period after ADH injection, i.e. within 3 - 10½ minutes.

It is interesting that the other polypeptide hormone from the neurohypophysis, oxytocin, produces a diuretic effect. Thus, as with the insulin - glucagon pair, two hormones produced from the same source with very similar chemical structures have opposing biological effects.

This discussion has obviously oversimplified the case for the seven minute cycle and its relation to the hypothalamus, and the neurohypophysical polypeptide hormones, vasopressin and oxytocin. There are complications in the

comparable times and actions from other hormones, like renin - angiotensin - aldosterone interacting system. Davis in (38) has summarized the evidence for a renin-angiotensin control of aldosterone secretion which includes effects on blood pressure and water retention. ADH is not mentioned. Gauer and Henry (39) also mention this, and indicate separate effects for ADH, aldosterone and the factor of vascular tone in controlling fluid volume.

They conclude that the fluid volume regulation is an integral part of overall cardiovascular regulation, which latter has hitherto been primarily considered with regard to adjustments of pressor or depressor activity affecting the heart and vascular wall tension. The control of the two systems seems to depend on the total sensory input from receptors in both low and high pressure regions. Evidence is presented which suggests that this input may be integrated into information describing the performance of the heart in relation to the load imposed on it ('competence' of the heart).

"Volume regulation activity has been judged from changes of mineral and water excretion by the kidney. It is concluded that the control of water and mineral excretion are relatively independent, and that the system (s) responsible for the regulation of water excretion are more sensitive and react faster than do those concerned with minerals. The equally important parameters of regulation of plasma proteins and blood cell volume have not been considered."

Davis' summary (38) is as follows:

"It seems clear that the efferent signal is the renin-angiotensin system and that angiotensin acts directly on the effector site, the zona glomerulosa of the adrenal cortex, to increase the secretion of aldosterone. Aldosterone acts on the renal tubule cells to promote sodium transport and, thereby, sodium retention by the kidney." (The author notes 'that chronic sodium retention is dependent upon an extra adrenal factor in addition to the high plasma level of aldosterone' referring to Davis, Circulation 25, 1002 (1962)). "Sodium retention is accompanied by retention of water and expansion of the circulating blood volume. According to this concept, the blood pressure and blood flow through vital organs including the kidney are increased. These changes would increase the stretch of the renal afferent arterioles and by this negative feedback mechanism would result in decreased release of renin.

"Such a control system provides a reasonable basis for the physiological regulation of aldosterone secretion. The effect of alterations in daily sodium intake on aldosterone secretion could be mediated by this negative feedback system which would thereby provide one of the primary mechanisms for transient acute changes in the rate of aldosterone secretion. In mild chronic sodium depletion, the evidence clearly indicates that the hyperaldosteronism is mediated by the renin - angiotensin system. It is likely, therefore, that a change in sodium intake from one day to the next and the associated alteration in aldosterone secretion are mediated by small changes in blood volume, arterial pressure, and renal blood flow and by release of renin."

The time of action of renin-angiotensin on blood pressure is shown in Page et al (22). Injection of angiotensin raises the mean blood pressure from about 110 to over 135 in 30 seconds or less, and the pressure then decays back to the pre-injection level in about 6 minutes.

"Renin induces a great increase in arterial pressure, sustained for over half an hour," the pressure rising from 115 to 170-175 in 8 minutes.

The angiotensin and renin curves both show clearly a 1-2 minute cycle in systolic and diastolic pressures.

According to the simplified mechanism in this popular article, "stress on the kidney stimulates the release of renin into the veins where it acts upon renin substrate (made in the liver) to release angiotensin I. 'Converting enzyme' changes angiotensin I to angiotensin II. Arteries carry angiotensin II to the capillary beds where arterioles are constricted."

From this chain of events, it isn't clear why the injection of renin takes 7 - 8 minutes to effect the maximum rise in blood pressure since the angiotensin directly causes a rise in a much shorter period. The decay times could be due to metabolic or absorptive removal of the active ingredients. The rise time of blood pressure due to angiotensin is in the order of a couple of circulation periods of the blood indicating that angiotensin could circulate once to bring out a second agent which then must circulate to a site of action. If only one circulation time is involved, then the time of action at the site may be several seconds in which case the action to constrict arterioles would likely be chemical rather than electric as with adrenaline.

It is more difficult to explain the delay time of renin action, and especially the fact that its effect ends up being higher than that of angiotensin itself. It may be that the delay time is due to a delay while angiotensin is being elaborated on demand.

It also isn't clear whether this system is operative normally to regulate blood pressure at the seven minute time scale. One might expect this to be true for angiotensin the seven minute cycle, and that renin acts to change the normal cycle during stress as suggested by Page.

The fact that two separate hormones appear to be active on the same mechanism (blood flow) at the same time scale suggests that the seven minute cycle may be mediated by one or the other or perhaps even by yet a third independent process, and the actions of these hormones take place in this blood flow cycle because the cycle is available and convenient. A good example of this is the blood circulation which is a carrier for all transported hormones, fuel and oxygen, and metabolic products. The circulation time cycle will be reflected in all the effects and concentration levels of all these materials.

It is equally possible that there is a separate demand signal from each major blood system tied to a particular hormone system which interact to bring more blood to the particular system when needed. For example, the renin-angiotensin system act on blood pressure to affect kidney blood flow. Vasopressin may act together with a chemical signal to decrease flow through the kidney, resulting in antidiuresis. A specific chain of events to determine a seven minute cycle is not known or speculated on now.

The interesting point, apparent in this case and in the higher frequency adrenaline case, but also to be noted later in thyroid, is that a low frequency agent apparently acts to shift the level of a higher frequency process. In this case, renin acting at seven to thirty minutes, shifts the mean of the angiotensin blood pressure effect to a more sustained effect. Later, it will be noted that

thyroid apparently shifts the high frequency adrenaline calorigenic effect to a higher mean level in a much more sustained effect.

Actually, this type of shifting effect can be considered down at the adrenaline calorigenic time domain itself. Thus, assuming the time domain of the metabolism to be rapid (Lundholm's cycle chain of lactic acid - CO_2 - vasodilatation at the seconds or functional seconds unit level), it is shifted to a two minute timed level by the adrenaline, not acting in the cycle chain directly but rather on one of the actions which produces one of the links in the chain. The result is a modulation of the high frequency to a slower frequency capable of a longer sustained slightly changed mean. It also appears that the longer the effect, the less the difference between maximum and minimum, and thus the more gradual the changes.

As a tentative hypothetical summary, regarding the near seven minute cycles, one may view it as follows: The hypothalamus - pituitary system uses vasopressin as a circulating hormone at a slow seven minute cycle rate to raise and lower the total blood flow. This implied that there is a localized oscillator cycle at the hypothalamus - pituitary cite, whose amplitude modulation is not guessed at at this time. The circulating vasopressin enters the various circulations, and, again on a local instability basis, forms a ring oscillator in skimming around the various major circulations (i.e. the blood systems 'twinkle' but now on a seven minute cycle basis).

There may be, in addition, labeled source hormones interacting with targets to assure that extra blood demand in any particular system will result in an adrenaline modulation at a slow rate to increase that local system's blood flow. It is possible that this labeled source hormone is used only to further augment a natural instability of the system to open up and take all of the blood flow.

Under these conditions, it is not surprising to find what appears to be source hormones operating through design lags at a slow near seven minute level. This keeps them away from interacting with the faster fundamental two minute cycle.

To close the operating chain, it is then necessary that signal from the local regions, each different - such as temperature from the peripheral circulation, lactic acid from skeletal muscles, chemical (renin?) from the kidney, chemical (?) from the GI tract, etc. - are received, through conversion, at the hypothalamus, which then splits its output signal into two paths, one to the pituitary to modulate, by choking, the entire blood supply, and the other to the autonomic nervous system to choke the local mean levels of capillary sensing. The action of source derived hormones may thus be quite separate.

The Thirty Minute Metabolic Product Release Cycle

It was the intention at the start of this report period to ignore this cycle or at least pay very little attention to it since its nature was not understood, and there was no obvious relation to hormone dynamics. However, the discussion of the basic oxidation reaction, sugar to lactic acid to carbon dioxide, and especially Lundholm's postulate of a lactic acid diffusion gradient from the cell to the tissue to the blood, has uncovered a possible mechanism for this cycle which may be very pertinent to the overall ventilation and metabolism process.

It appears likely that this cycle is a result of the same process mechanism that produces the sustained vasodilatation effect (noted in Barcroft and Swan) with administration of adrenaline, which was discussed previously. On injection of adrenaline, there is a transient vasodilatation which reaches a maximum in 10-20 seconds followed by a fall in a minute or so to a level about twice the pre-injection level which then takes 20 or more minutes to decay back to normal.

A mechanism for this action time of something over 20 minutes is suggested in Lundholm's thesis that the added adrenaline stimulates an increased production of lactic acid in the cells which results in a higher diffusion gradient for lactic acid from the cells to the tissues to the blood, and that it can take an extended period for the diffusion gradient to decay back to normal. Thus, it would take a similar period for any change in CO_2 concentration to decay back to normal.

Now, this 20 - 35 minute cycle has also been found in the ventilation rate of the lungs. It was suggested that the cycle was a result of CO_2 diffusion times from the blood to the higher nervous centers, probably via the spinal fluid (or perhaps across the blood - brain barrier is implied). It now appears that a cycle of this period is possible, not due to CO_2 diffusion lags directly, and not necessarily tied to higher nervous centers, but simply by a lag time in the diffusion of lactic acid. This results in a secondary CO_2 lag which shows up in the ventilation as a 20-35 minute cycle.

The alternative mechanism suggested previously for the sustained vasodilatation may serve equally well as a mechanism for this cycle generally, namely that there are two adrenaline effects. One is a transient of one to two minutes duration due to the adrenaline injected into the blood stream from the outside or from the adrenals, and the second, a more sustained action resulting from the slow liberation of adrenaline which had been previously absorbed from the blood onto various binding sites around the body.

The net effect of this 'sustained' adrenaline effect would still be to produce a longer period sustained rise in lactic acid leading to CO_2, vasodilatation, and a 30 minute cycle in ventilation and metabolism.

This 'binding site' idea suggests a mechanism for the long time delay actions of hormones like the thyroid. It has been worrisome that a hormone, injected directly into the blood, could take days to produce its maximum physiological effect. However, if these hormones are immediately absorbed on blood constituents or binding sites in the organs, and then metered out slowly, a long period action time is thus produced.

The Three Day Water Balance Cycle

As noted in (1), a three day cycle was found associated with body weight. Since the food intake was approximately constant, the weight cycle was probably related to water retention, and thus represented a water balance cycle.

Similar cycles are shown in Newburgh (26), in relation to water retention as a factor in the apparent transient inbalance of calorie intake and weight. Thus, it was shown that the weight does not reach the predicted level (based on a calorie intake versus metabolic heat loss) until weeks after the diet starts. The high frequency three day cycle is clearly indicated but not discussed as a

significant basic system cycle. Other sources such as Asper (40) show beautiful three to four day cycles in metabolic activity and other indices.

The hormone which is most likely involved in this cycle should have a time of action in this time domain, either by having a slow rise time or a slow decay time. It was readily found that the thyroid hormones apparently act only after time lags at this time scale. For example, Logan and Lain (41) give the following oxygen consumption for guinea pigs under anesthesia after a single injection of thyroxin:

Time - hours	Increase in % O_2 consumption over pre-injection mean
4	5.9
8	14.4
12	14.8
16	15.0
20	16.7
24	19.6

A maximum increase in oxygen consumption had not been reached in two days.

Rawson et al compared the action of triidothyronine and thyroxin on a myxedemous patient. The basal metabolic rate was measured over a two month period. A five day cycle or thereabouts is apparent in the basal metabolic rate. Triidothyronine exerted a prompt but short lived increase in the BMR (the rise appears to take about two days to reach a maximum), and in the excretion of nitrogen, phosphorous and creatin. "Thyroxin exerted a slow and prolonged effect on the same indices. If one disregards time of action, there were no qualitative differences between these two agents. Quantitatively, on an equimolar basis, the only differences are in the speed of action. The differences in the speed of action of these two agents can be correlated with the rate of disappearance of each agent from the circulation".

Rawson and Sonenberg (43) state that myxedema treated with desiccated thyroid produces a diuresis in the first 2 - 3 days. In 10 - 14 days, the BMR rises to a normal level. Triiodothyronine is 3 - 5 times more effective than thyroxine. The BMR reaches a maximum in 9 days with thyroxine and in 2.1 days with triiodothyronine.

Van Middlesworth and Intoccia (44) show clearly a 3 day cycle of iodine excretion in the feces.

With this clear indication of a two to three day lag in the thyroid hormone action (even considering triiodothyronine, the fast reactant) it is considered plausible that the primary action of the thyroid hormone is on some aspect of the water retention cycle. This water retention cycle likely involves a complex of water-food-electrolytes, mediated by thyroid secretion. This is indicated also in the cyclic excretion of nitrogen, phosphorous, and creatine. Further substantiation is provided by Rawson and Sonenberg (43) observation that diuresis is produced in 2 - 3 days on treatment with the thyroid.

On the other hand, Lloyd and Lobotsky (45) state "The thyroid gland plays a minor role in maintenance of normal water excretion. Absence of normal thyroid function tends to produce a drop in glomerular filtration and a sluggish

response to water. Under normal circumstances, it does not appear likely that changes in thyroid secretion contribute to the production of diuresis."

It should also be noted that aldosterone and corexone affect fluid intake. Gross and Lichteen (46) show a clear 3 day cycle in fluid intake and weight rise. Corexone and aldosterone increase the amplitude of the waves.

In the previous section, it was noted that there is apparently a relation between renin - angiotensin and aldosterone. It appears these three (plus the angiotensin II and the enzyme in the system) are related in activity, and yet they apparently act in different time domains, the angiotensin in a seven minute time domain, the angiotensin in a seven minute time domain, renin in a time domain greater than thirty minutes, and now aldosterone in a cycle of two to three days.

It is very likely that a similar relation holds in the metabolism - with adrenaline acting at a two minute cycle, lactic acid at a thirty minute cycle not necessarily associated with a particular hormone but with metabolic by-products, and the thyroid at two to three days.

It has been claimed that thyroid has an influence on vasopressin action. However, as noted in Lipsett et al (47), "the alleged thyroid-induced decrease in the sensitivity of the renal tubules to ADH (Smith 1951) has been supported (Weston et al, 1956) and disputed (Epstein and Rivera, 1958)." It would be nice if a calorigenic action was also found for vasopressin. There would then be the complete progressive calorigenic series of adrenaline, vasopressin, and thyroid.

This shift of limit cycle behavior was discussed in (1) in connection with temperature cycles on exposure to cold. In that case it was pointed out that "a point-wise disturbance in space - a finger - or in time - cold immersion for a certain period - can create both transient response and shift limit cycle behavior."

It is likely that this shift in limit cycle behavior is the prime action of the hormones in a series that goes progressively from short time domain to longer ones. The action of each new hormone is not just another direct interference in the basic chain but more likely a shift of operating level by an extraneous action that affects one or more of the components of the basic chain.

For example, it was suggested above that the basic calorigenic chain - as proposed in Lundholm is a glucose - lactic acid (in cell) - lactic acid (outside cell) - CO_2 - vasodilatation, with two physical steps left open, one that lactic acid is only produced from glucose in the action of muscle discharge, and a second that the vasodilatation leads to a more rapid removal of CO_2 and lactic acid, and thus to vasoconstriction. Adrenaline then influences this chain by affecting the mechanical element of muscle discharge which leads to increased lactic acid - CO_2 and an increased heat production in an adrenaline 2 minute cycle. Thus adrenaline acts to shift the faster 10 cps cycle on a two minute modulating level. Now thyroid modulates this cycle to a still longer one at periods of 2 - 3 days, probably by effects on the water make up of the whole organism.

That thyroid acts to modify the adrenaline action is not a new idea. For example, Hoch (48) states, "The thyroid hormones are thought to regulate the magnitude of the calorigenic, glycogenolytic, and hyperglycemic actions of

epinephrine (Ellis, 1957). Increased amounts of thyroxine potentiate, whereas decreased amounts of thyroxine lessen or abolish some of the actions of epinephrine. This implies that epinephrine is in these instances the effective primary agent controlling cellular metabolism, and that thyroxine acts in a secondary role.

"Indeed some conclude that the peripheral effects of large doses of thyroxine may all be mediated via epinephrine."

Other comments by Hoch are:

"Thyroxine is reported to potentiate the calorigenic and metabolic effects of adrenal meduallary hormones by inactivating the enzymes which inactivate the adrenal hormones."

"Whereas the hyperglycemic response to epinephrine may be reinforced or diminished by previous treatment with thyroxine, the 'calorigenic' response to epinephrine is potentiated by thyroxine."

In conclusion, Hoch states, "the evolution of a picture of the biochemical actions of a hormone at the present time is limited by our inability to resolve the molecular events in situ in the living cell. Lacking this, conclusions must be drawn inferentially."

That thyroid may affect epinephrine action is also indicated in Wurtman et al (49). They show the effect of l-epinephrine on mean blood pressure in hyperthyroid, hypothyroid and normal male rats. The blood pressure in all three cases, rise rapidly in 10 seconds after injection of epinephrine to maxima of 35 mm. for the control, 40 mm. for hypothyroid, and 80 mm. for hyperthyroid animals. The blood pressure of the controls decays back to normal in 60 seconds; of the hypothyroid in 70 seconds, and of the hyperthyroid in 100 seconds.

Thus it is likely that thyroid plays a secondary role in the calorigenic process. It is not likely that this is an effect on the basic enzymes as suggested in Hoch either of the muscle action cycle or of the adrenaline cycle, as then one would have to fit a cycle several days long into the probably relatively rapid enzyme action. It is much more likely that a shift in water balance as noted below affects relative rates of build up of lactic acid, thus affecting blood flow and metabolism very indirectly.

The thyroid cycle involves at least one additional factor which has been discussed in (1); namely, the relation to the thyroid stimulating hormone. There is apparently an interrelation between the thyroid stimulating hormone (TSH) and the thyroid hormone by which TSH stimulates secretion of thyroid, and is itself inhibited by the thyroid hormones. Danziger and Elmergreen (50) proposed a mathematical theory of thyroid - pituitary interaction. The summary to (50) states (1956):

"The paper develops a mathematical theory of thyroid - pituitary interaction. It is assumed that the pituitary gland produces thyrotropin, which activates an enzyme of the thyroid gland. The rate of production of thyroid hormone is considered to be proportional to the concentration of that enzyme. It is further assumed that in the absence of the thyroid hormone, the rate of production of thyrotropin is constant, but in general it is a linear function of the concentration of the thyroid hormone. This picture leads to a system of non-linear dif-

ferential equations, which present great difficulties. This system, however, may be conveniently 'linearized' by considering that the relations between different variables are linear, but that within different ranges of the variables the coefficients are different. Using this approximation, it is possible to show that the system admits periodic solution of the nature of relaxation oscillations."

The equations used by these authors should be examined in terms of the three day cycle. As a first thesis, it is possible to conceive of a cycle in thyroid hormone based on the TSH-TH interaction.

Thus it is possible to postulate that the thyroid hormone concentration in the blood oscillates in cycles of three days, producing changes in water content of the body. At this time domain the primary action is not likely to be on enzyme systems. It could however be "the result of changes in permeability of mitochondria" as attributed to Tapley and Cooper (1956) in Pitt-Rivers and Tata (51), if these mitochondria are especially sensitive to small changes in the total water content in the body.

It is of interest to inquire where this water may be coming from, i.e. from the blood, from the intercellular fluid, or from the cells. For an effect on mitochondria, one would expect the water to be coming from the cells and changing the intracellular concentrations.

According to references cited in Pitt-Rivers and Tata (51) "administration of thyroid extract or thyroxine effected a transfer of water from the tissues to the blood, thus increasing the total blood volume by 25 - 30% (Thompson, 1925; Fujimaki & Hildebrant, 1924). It therefore appears that the diuresis of hyperthyroidism is secondary to dilution of the blood." Results reported on effects on electrolytic transfer are inconclusive because of the high doses used.

Thus following Lundholm, the effect of thyroid on metabolism is likely to be an effect on the relative rates of rise of concentrations of lactic acid in the intracellular and extra cellular fluid and the corresponding diffusion gradients. If the intracellular fluid volume is small, the concentration rise of lactic acid will be rapid. Since the extracellular fluid volume is high, the concentration outside will rise more slowly. Thus, for the same number of muscle discharges, producing the same quantity of lactic acid, the concentration gradient will be higher, leading to more rapid transfer of lactic acid to the extracellular fluid with corresponding more frequent CO_2 levels and more frequent capillary openings and a higher oxygen supply, and a higher metabolic rate.

The changes in metabolism due to thyroid are apparently in the 20 - 30% range. Changes in water level, if they involve a number of pounds of water in a total of 20 lbs. of blood and extracellular fluid is of the right order of magnitude though more detailed study will indicate how close the correlation really is.

Another possible mechanism is that the thyroid action in water balance may be tied to the central nervous system, and particularly to the hypothalamus. Anderson & McCann (52) have shown that polydipsia is evoked by hypothalamic stimulation either electrically or by injections of a 2 - 3% sodium choride solution "into a fairly limited part of the hypothalamus of a goat." The authors report that whereas the salt solution injections sometimes caused polydipsia and sometimes did not, polydipsia could always be produced "by electrical stimulation of

a discrete region of the hypothalamus ... Drinking caused by electrical stimulation commenced 10 to 30 seconds from the onset of stimulation and stopped 2 to 3 seconds after the current was discontinued. Tremendous over hydration could be induced in this way followed by marked hemodilution and polyuria. When tested in one experiment, the stimulation at the same point where polydipsia was evoked produced a marked andiuresis of neurophysical type."

Thus the effect of thyroid may be an effect on the nervous system resulting in changes in water balance.

That shifts in water balance may influence metabolism is not too surprising considering that metabolism is essentially the reaction of oxygen with sugar to ultimately form CO_2 and water, all in aqueous solution.

Summary

a. A study has been made of the possible hormones involved in four cycles considered of basic importance in the operation of the human. These are the two minute heat production cycle, the seven minute blood flow cycle, the thirty minute by-product cycle, and the three day water retention cycle.

b. It has been postulated, in connection with the two minute cycle, that the muscle fibre is an unstable system which will fire in ever increasing numbers to a catastrophic running away level, if unlimited oxygen and fuel is available. The choke on this engine is the oxygen supply which is metered to the muscle cells in a two minute cycle of blood flow in opening and closing capillaries. This mechanism has been further evidenced by the effect of high oxygen pressures on animals which result in tremors and convulsions leading to death.

d. Based on its calorigenic effect, its vasodilatation effect primarily in skeletal muscles, its effect on muscle discharge, and a time of action for the transients of about two minutes, adrenaline (epinephrine) has been postulated as the hormone mediating this heat production cycle.

d. Following Lundholm (31) the adrenaline effect is produced by increasing lactic acid which produces CO_2 which causes a vasodilatation of the capillary which washes out the lactic acid. It is suggested here that adrenaline acts electrically to cause discharge of the muscle cells which results in the formation of lactic acid.

e. The two minute cycle thus does not depend on the two minute adrenaline cycle but rather on the delay times of lactic acid diffusion out of the cell followed by the build up of CO_2 to trigger the opening of the capillary and its filling with arterial blood.

f. The seven minute cycle is a blood flow cycle, mediated from the hypothalamus possibly by vasopressin. The vasoconstricting action of this hormone may be more important in this respect than the action in the tubules. Alternately, it has been suggested the oscillations in flow produced in the kidney are reflected in flow cycles throughout the circulatory system.

g. It has been noted that angiotensin affects blood pressure in a seven minute action and that the renin - angiotensin - aldosterone interacting system may be equally considered to be involved in a seven minute cycle.

h. The three day water retention cycle has been tied to the thyroid by virtue of this hormone's long time action.

i. The calorigenic action of the thyroid hormone is considered to be secondary to its effect on water balance, which may effect relative concentrations of lactic acid in the intra- and extra-cellular fluids. It has been suggested that the site of action of the thyroid hormone could be in the kidney, or to shift water from inside the cells to the plasma.

j. The insulin - glucose interaction has been discussed as an excellent illustration of oscillator regulation of a prime homeostatic mechanism.

k. It has been noted in the adrenaline-thyroid calorigenic effects and in the renin - angiotensin - aldosterone blood pressure effects that the major action is for the lower frequency effector agent to shift the stability of the higher frequency limit cycle, to cause a slower oscillation of the mean. This is apparently a basic mechanism throughout biological systems and may well serve as a guide to the study of apparent complex and highly redundant mechanisms and processes.

It has been noted that these cycles can be related simply to the basic oxidation equation in biological systems. The basic equation may be represented as

$$\text{sugar} + O_2 \longrightarrow CO_2 + H_2O.$$

The adrenaline action is thus effectively an O_2 choke; insulin is a sugar choke; the thirty minute cycle is a lactic acid - CO_2 delayed elimination cycle; vasopressin is probably a water regulator in the seven minute time domain; and thyroid produces a water balance on a three day cycle level. These hormone actions can thus be considered as separate flow controls of the components of this basic reaction. Though the raw materials and reaction products are all carried in the same overall blood stream, their flows can be considered as being essentially independent. (This is a common technique used in chemical engineering process controls to consider separate component flows and actions independently even though they are in one stream.) Thus, there is an effective oxygen flow, a blood flow, carbon dioxide-lactic acid flow, and a water flow superimposed on the essentially aqueous carrier stream. If this picture is correct, there are likely flows of electrolytes, fats, amines, etc., and these flows may also have individual hormones for the separate flow controls.

It also appears necessary to postulate two actions for each effect; one, an idling action for the entire system in which all parts of the organism share in the separate flows at a base level - according to some division based on base need; the second action is a means for providing increased flows to a portion of the system when that portion has increased need.

The possible technique is one of making the individual systems marginally stable, so that the system in need can begin to hunt and demand more than its normal share. In general this instability is likely augmented by chemical signal. It is not clear whether the chemical signal acts locally or is delivered centrally as an electric signal.

So far, in viewing the overall complex biological system like the human, the following fairly firm points regarding the system, that can help in decoding the behavioral system, are adopted.

a. The system is made up of a large number of internal oscillator systems.

b. These systems, each of which have an autonomous oscillator at its base, act within a wide spectrum of separated time effects.

c. Typical responses are a first order reaction from one level to another, or a second order reaction from one level to another.

d. Most of the oscillators are mass flux monitored (i.e. 'choked') as a feed to an unstable element.

e. Generally, with a rate governing reaction that governs the input mass or other flux intakes, the oscillating instability is sequenced around in the system on a near random basis (although preferential orders develop).

f. The oscillators tend to be electro-chemical.

g. The first and second order reactions tend to be chemical-mechanical.

h. The electrical communications signalling tends to cluster around the 10 cps level.

i. Hormones tend to monitor one or two stream, more likely two stream reactions, where they act as small signal catalysts.

j. The local oscillator frequencies tend to be higher, and nearly the fundamental high frequency in each system.

k. The system then has sensors that send signals through the nervous system to other oscillators that modify the system characteristics.

l. There is a slower level of signals to the hypothalamus that regulates intersystem characteristics (i.e. it remains as an intersystem synchronous switchboard).

m. The nervous system as a whole senses the state of all systems, and operates with switching algorithms to affect changes in the systems.

n. Below the level of the hypothalamus, the medulla operates with independent switchboards that regulate local systems according to simple algorithmic intrasystem routines. Thus the actions of hypothalamus and medulla represent an 'additive' type of parallel logic, with the hypothalamus the supervisory type of autonomic (i.e. automatic) logic.

o. It is likely that the thalamus is the gateway to executive type of logic, whether conscious or subconscious (i.e. material under control of an algorithm that developed within the history of the system). At this time no specific function is assigned to the thalamus.

p. There are short term 'reactions' involving the nervous system (i.e. the chord system) that proceed on very short paths from an input signal to nervous system, centrally into the nervous system, to a signal output from the system to some motor element. These take place at the near 0.1 second level.

q. It is premised, contrary to common ideas that this is transit time determined, that this is more nearly time determined to be a path length that uses up this time in transit time; that such a system is used to keep information synchronous with a basic local repetition rate of near 10 cps.

r. The freedom in the system to make 'conscious' decisions is quite illusory (just as is most of the so-called freedom that the executive is commonly endowed with). However, this idea must be disentangled within a complex framework. The individual 'cycle' hunger response is voluntary (whether in ventilation, food, water, sex, heart rate, etc.). This thus is under nearly as much 'conscious' or 'emotional' control as it is under 'involuntary', 'autonomic', or automatic control. As one averages over slower and slower 'cycles', whether fully periodic, or aperiodic bumps, generally there is some time domain at which the greatest degree of decision making freedom exists. Beyond that, succeeding averages tend to become more deterministic, and the more nearly does behavior resemble a temporal twinkling about mean states. More nearly, the ergodic assumption may be selected, so that the individual performance twinkles about, within a relatively narrow band that describes a considerable segment of human behavior. (The most shocking illustration of this was proposed in weight control. The individual's caloric intake, say averaged at least to the weeks-months level, is essentially determined. The individual's activity level is determined as part of the long range developmental algorithm. This is meant literally, not as any poetic, or philosophic figure of speech. For example, we have noted, among a few hundred men who are exercising quite 'strenuously' in the city of Cleveland, for as much as 5-10 hours per week, that essentially equal time is devoted to extra resting, so that the net activity level is not much higher than normal, and there is little guarantee that very many will do anything but 'twinkle' at activity for a long period of time. Weight thus rises over the months-years level to where the calorie output for the activity level with the heavier body rises to meet the physiologically determined calorie input. Averaged over a number of years, and over a number of people, one quickly gets quite narrow 'normal' responses for the species. See for example, Fig. II-1 of data from Johnson and Karl, 1947 (27), which indicates a fairly closely associated variation of 'voluntary' caloric intake with temperature).

s. The framework for human behavior must be the far-from-free 'conscious' and 'subconscious' developmental algorithmic content that the human species developes, that rides within the nervous system on top of the thalamic structure, and that has its more automatic control centers in the lower portions of the nervous system of hypothalamus, medulla, and chord structure.

t. It is much to the point, in seeking a codification of behavior, to view it from the eyes of the master psychiatrists and psychologists. (In a subsequent second report, the system will be viewed from the point of the neurological and neurophysiological masters, then later, likely in a third report, some original experimental research will be begun to probe at communications models for the brain-body structure). At the present time, within the previous reports, key words that have been uncovered have included:

sex system	stimulus	gestalt	anger
association	simultaneity	erogenous zones	thought
reinforcement	habit	consciousness	memory
evolution	inhibit	activity	hypnosis
pleasure-pain principle	conditioned	attention	neurosis
self maintaining mechanism	reflex	agression	dreams
unconscious	sexuality	melancholia	sublimation
repression	libido	death instinct	language
resistance	ego	free association	sexual drive
transfer	hysteria	slips	drive
admiration	schizophrania	phantasy	tension
censorship	synchrony	reproductive drives	diminution of excitation
distortion	orbital synchrony	oral eroticism	drives
sleep	self-preservative drives	anal eroticism	reversal into opposite
turning round conversion	compulsion	sadistic	play
circulating ideas	time binding	masochistic	eat
id ("es")	tendency to repetition	superego	sleep
elimination functions	psychoses	love	fear
emotional response	obsession	conscience	conflict
reverberating loops	delusion	cortex	mind
neural nets	threshholds	brain	

The following represents a brief effort at codification!

Freud - Libido Theory of Psychosexual Development

Greenson (53) is used as a brief summary source.

Oral Phase 0-18 Months. Characteristic pleasurable body zones involving mouth, lips, tongue, stomach, with sucking, and then biting as the most pleasurable activity. No distinction between self and nonself. Relationship to objects is autoerotic, narcissistic, preambivalent (neither attracted nor repulsed). Skin, temperature sensations, equilibrium sensitivity are secondary important sources of satisfaction. (In summary, by the pleasure-pain principle, the infant is mainly directed toward a very limited number of 'satisfying' activities; i.e. activities in which the system locks in with or synchronizes with).

Anal Phase 18-36 Months. Characteristic pleasurable body zones are anus, rectum, and bladder, with excretion and retention as the most pleasurable activities. If parents interfere with these pleasures (as is done in our society), the child's relation to adults become ambivalent. Attitudes concerning behavioral routines, as well as submission, anger, defiance develop in accordance with the system's resolution of the need for parental 'love' satisfaction (an orbital attachment and synchrony) and for instinctual satisfaction (another orbital attachment).

(In summary, two large 'satisfying' complexes, both of which require considerable system synchronization, in time and effort and in the number of cooperative internal motor operators, are in conflict at a period in which the system is undergoing significant algorithmic development. The specific primitive content of much of the behavioral reactions and routines later develop here. The

keynote is not the primacy of the anal phase, but the conflict is between major pleasure attractions that invoke many motor operators. The basic problem is that not all decision making involves many motor operators, so that a conflict during this phase is quite real.

As a matter of fact, out of this one point arises the beginnings of a major theme regarding behavior. If the medulla is completely wired for system routines, and the hypothalamus is coded for intersystem routines, it now appears that the higher system algorithm (the 'cortex') is left essentially open with regard to the executive logic which actuates the system into loosely synchronized orbits.

The system behaves, not like a molecule wandering in a random walk through its peers, but like the free electron theory of metallic conductivity - see Frankel (54) Section 31, and 34 - locks in and makes a number of revolutions or oscillations at each attracting center, before breaking off and going on in its 'random' walk. A helpful factor in such a system is some weak attracting force, like Coulomb attractive forces, which will lock the system at long range but weak orbits. A good example of this multiple oscillation path is supplied by a pin-ball machine, which can serve as a first prototype - in complex enough form - for behavioral modelling.

The human child is thus an adaptive computer, but really so. It has not learned its major motor system routines, nor are they programmed. Yet the maturation developmental unfolding of the system, the presence of parents, some pleasure drives, etc. furnish attractive forces and an external milieu in which the presence of conflicts set up the 'executive routines. Thus one finds built in the first 'routine', if its put near your mouth, suck on it, or if you are a chicken infant, if its put near your mouth, peck it!! Then there is a developmental interactional unfolding of a more complex executive routine. These ideas are of course only the most primitive beginning, but they are a beginning at a behavioral system modelling.)

Phallic Phase 3 - 7 Years. Boys and girls differ. The boy's characteristic pleasure zone involves the penis. Internal fantasy, the Oedipus complex, involves strong 'love' attraction to the mother, and hostile rivalry to the father. In the girl, the main characteristic pleasure zone involves the clitoris. Masturbation is for both boy and girl a primary pleasurable activity. There is an internal play of penis envy. The mother is renounced as the primary love object, as blame for lack of penis, and instead internal fantasy and attraction for the father. Anxieties in both cases - a fear of castration in the boy, and a fear of losing parents love in the girl, leads to a latency period in which these conflicts begin to be reconciled and resolved.

Latency Period 7 - 12 Years. The Oedipus complex is resolved in favor of a cohesive censor structure, the super-ego that develops a set of decision values, 'good' and 'bad'. Great strides are made in 'intellectual' and 'physical' accomplishments. The infantile sexual interest recedes and is secondary to handling agressive impulses. Group formation and hero worship outside of family begins.

(Bravo, Sigmund Freud. Once again a tremendous wisdom begins to show up in organizing a physically feasible system. If the system meanders by orbital synchrony, and weak forces are needed to trap orbits, and an executive logic structure has not been supplied at the beginning, it is necessary to be fairly

certain of developing one. The algorithm of, if its near your mouth suck on it, and the counter pleasure-principle in the mother (plus the entire complex that has not yet been uncovered) assures orbital attachment between these two. The best 'proof' that the forces of attachment are weak forces, so that the mother-child attachment is not some mystic necessity, is shown by the fact that it need not even have to exist. A most provocative article discusses a not-uncommon brutality of parents to children (55). However in the more general case in which it exists, it is clear that the child is thrown into attachment to parents, particularly the mother, or perhaps more realistically, with attachment to the mother, and thus in contiguity with the father who is sexually attached, orbitally to the mother. The odd-ball role requires a readjustment of orbits. It comes as no surprise that infantile sexuality tends to furnish captured orbits, first to the mother, by virtue of the sucking-feeding response, and then later on a reorientation by virtue of a sexual orientation of boy-woman, girl-man. The authors will not judge nor are they clinically competent to judge the strength and complexity of the attachment. That must come later. However, the fact that only weak orienting forces are needed makes Freud's general probing quite useful, whether it is or is not 'exact', or 'overstated'. It tastes 'right' to the authors as physical scientists.

Now, for the mysterious- at least at this time - ingredient, the plasticity of the maturing brain is prepared to accept the more final molding of decision-making logic by virtue of the orbital associations with the 'loved' or attracting parents. Freud called this the super-ego. Well and good. It is not a metaphysical or imaginary concept, but hypothetically, a complex algorithm that forms in these years that take over the executive logic, that such a structure as the hypothalamus cannot perform. It is here that the keys of behavior - in the sense used in our original May 1962 proposal, p. 26-30 - must lie. The key thought that one derives from the Freudian scheme is that within the age range, 7 - 12 years, the executive logic is formed, that, somewhat different than Freud, it is not a moral structure of 'good' and 'bad', but an expedience structure that makes decisions that seem 'good' for the organism or 'bad' for the organism. The tags, good and bad are not the relevant item. What is relevant is that the structure of 'good' and 'bad' decision making, or 'do' and 'don't do', or 'go' or 'don't go', etc., i.e. all the dichotomies of action, is made in conformity with what are the pleasurable directions of infancy, and the earlier years. Here lies the foundation of human irrational behavior!!!

What is not being bought or sought is the Hegelian metaphysic in Freud, but the sane, sound, cold, near-neurological clinical logic that lies underneath the Viennese frosting.

As was guessed as a hypothesis, the 'cortex' acts to put out the hypothalamus fires. The presence of absence of nervous signalling fires is what represents the pleasure-pain principle. There is first found accidental and random associations of signals with particular behavior in infancy. A few instances are not enough to fix the response. Repetition finally overcomes a threshhold and isolates a specific behavior as being more 'pleasurable' than another in taking care of the 'fires'. These become preferred coordinated complexes in time. The temporal unfolding of the order of systems that contribute large numbers of signals, or high intensity signals takes place. First the sucking and eating system. Then the voiding systems. Finally the sexual systems. There is an order of maturation in the nervous system by which the primacy of central signalling reponse makes itself evident. Thus the growth of activation from mouth, to stomach,

to excretory organs, to sex organs. 'Pleasure' and 'pain', that arises from the dichotomies of action - one must note that all of the actions, to suck, or not to suck; to eat, or not to eat; to void, or not to void; to masturbate, or not to masturbate, - are all dichotomies that vary nervous signalling content - are represented as nervous fires. The ideas of which of these individual system states are to be preferred develops by association, repetition, contiguity, etc. in infancy, the behaviorist thesis, but the organization and integration into the command logic for the individual doesn't take place until later, as the 'super-ego', the Freudian thesis. The 'ego' represents the totality of signalling 'drives', i.e. nervous signalling complexes, as they make themselves evident at the 'hypothalamus'. All of this of course has not proceeded one step of the way along the neurological modelling of the problem, but it helps create a physical system, that could be modelled as a precursor to examining the nervous system. We are now convinced we have finally put a very thin foundation under the problem of behavior. Out of context, the ideas may not be new. However the assembly is somewhat new in creating an overall physically feasible, consistent, and thus defensible view. Kindergarten is abruptly ending).

Puberty 12 - 14 years. (Not comments at this point).

Adolescence 14 - 20 years. Educational upheavals, quick changes; revived sexual preoccupation; romantic infatuation, rebellion against authority; seeking intense emotional experience; radical idealism, intellectual hunger. Hormonal changes upset the previous equilibrium. Out of conflict, there are triumphs of 'instincts', 'conscience', or 'reality'.

Psychoanalytic theory approaches behavior and its distortion (neuroses) as dynamic, genetic, topographic, economic, and structural, five distinct points of view. Other psychologies use only one or another of these.

Topographic. Mental phenomena exists at other than the conscious level. This can be seen in dreams, errors, and symptoms of neuroses. (True. We interpret this to mean that there is an internal computer that senses both the external and the internal system, and that can lock into internal 'dramas' and 'fantasies' that represent dynamic states of the internal system).

Genetic. Present behavior can only be understood in terms of the past, and as a result of interplay with biological structure. (Obvious).

Dynamic. Behavior is result of interaction of instinctual impulses impelling toward gratification, and counter-forces opposing gratification in favor of security or self-esteem.

(We here disagree, and are not even convinced that the idea is Freudian. The two categories are on different levels. 'Gratification' is on the nearer instantaneous nervous signalling level. Stimulating a goat's hypothalamus will make him 'gratify' his thirst by drinking up to 40% of his body weight. Seeking security and self-esteem, part of the internal fantasy structure of the 'super-ego', is a strategy of 'voluntary' behavior. This is just an over-simplification of the complex executive logic, that somehow optimalizes its 'gratification' structure. It is not an example of dialectic thesis - antithesis, but of complex physical dynamics).

Economic - The organism has a limited quantity of energy at its disposal for disposal among psychic factors. (Same comment. It may be a fact that

the bandpass for the hypothalamus is finite, and the limiting factor, or it may be a fact that the number of neural paths in the cortex, or spinal chord, etc. is the limiting factor. Statements about a limiting quantity do not contribute any picture to how the networks divide their tasks, what the executive logic controls, and what are the flow limiting factors in such divisions. It is clear that 'trivial' psycho dramas may at times use up all the available channels of the human. However it is far from clear that such a status represents 'normal' system operation in all but the most violent extremes).

Structural - The structural division is into id, ego, and super-ego. The id is the instinctual reservoir. It is unconscious. Only derivations of the instinctual impulses gain access to the consciousness. The ego is the control apparatus for psychic judgment. It is responsible for perception, thinking, memory, and judgment. The super-ego is the conscience and ideal. (As poorly named structures for functions, we will accept this term. However, it would seem better to view the 'id' function as the hypothalamus structure plus its signalling connection toward higher centers. The functionally controlling computer-controller system that deals with the states of the system may be regarded structurally as the cortex. The super-ego function represents the executive logic that develops in the cortex to perform the non-automatic control. This much simpler, more primitive almost naive view, is one that does not do violence to the Freudian scheme, but that can be used for a first orienting view of structure and function associated with structure. Why this is better today than in Freud's day is that more is known about what can be done physically in a control and computer control system).

Neurotic conflict is represented as a conflict between forces of the id and the ego.

(It comes out much better, if the id represents the total complex of internal oscillator responses that exists, say at the hypothalamus, and which then has an 'ego' imprint into a higher center, and that the dynamics of the higher center, the 'ego' function acting under super-ego algorithms, does the controlling. This is a slight shade different from earlier reports, but the semantic differences are over the nature of the total extent of the 'ego'.).

As a reasonable guide to the ideas and philosophy of psychoanalysts, a very good exposition by Munroe (56) was used. Its advantage, stressed in the preface, is that she writes as a psychologist, with sufficient background to immerse herself into each school, and in addition her manuscript was critically reviewed by many psychological and psychiatric masters. This general guide was augmented by specific material by Klein (57), Sullivan (59), Horney (61), Alexander (62) and Arieti (63).

M. Klein's Theoretic Views

Klein's views were sought in greater detail in (57). Her "contribution to psa theory as a whole derived from the play technique evolved with young children". Whereas, it had been held that psa suitable for children in or beyond the latency period (7 years on), she started on young children. The psa play technique was begun because children expressed their fantasies and anxieties mainly in play. This play became the Freudian free association technique adapted to children. Also guided by the Freudian tenets that exploring the unconsious is a main psa task, and that analysis of the transference - in this

case to the play content - is the means of achieving the end.

The play content, in children down to 3-5-7 years, showed obsession, transference, self-image, other-image, anxiety, sexual activity, fantasy, agressiveness, guilt, parent image, sibling image, fear, depression, love, anger, frustration, jealousy, hate, repetition of experience, interweaving of fantasy and reality, repression, inhibition, symbolism, death feelings, genital views, response to interpretation, defense against anxiety, harshness of super-ego in a three year old (i.e. it begins much earlier than Freud supposed, and develops as an end product over many years), and internal imagery. In analysis of little girls the major female anxiety is over the mother who is viewed both internally and externally as the prime persecutor (The girl in fantasy attacks the mother's body, taking things from it and is in fear of retaliation. The persecutory anxiety alternates with depression and guilt, and a tendency to make reparation. This tendency is the main contribution to all sublimation.) One finds anal-urethral, and oral-sadistic impulses. The early super-ego builds up when the oral-sadistic impulses and fantasies are at their height; Castration fear is the leading anxiety in boys, but the early identification and relation with the mother(which ushers in the Oedipus complex) molds the anxiety about attacks on the inside of the body and the castration fear; The origin of the psychotic anxiety nature of bodily attacking and being attacked externally and internally is traced to oral-sadism, in common prototype to the mother and the internalized view of a devoured and devouring breast. This internalized view of an injured, dreaded, or satisfying, helpful breast is the care of the superego.

(Thus note the beginning 'confirmation', admittedly in a Freudian view, that the executive logic starts with the cortical direction of sucking on it if its put near your mouth, and that as each physiological system begins to be fully operative in a maturing sense in its connection with the nervous system, occupying an increasing share of the 'hypothalamus' switch board effort, the generality of the cortical logic distribution shrinks, becomes more localized, and the more systems response become imprinted and localized in their conflicting executive decision making logic. By age '7', the logic as a whole has received its first overall coordinated development. Thesystem has a loose but essentially 'complete' executive logic, that now can control 'hypothalamus' fires. Good, bad, or indifferent, this will represent a first model of behavior which will be probed at against the neurological background of the nervous system). These represent most of the key ideas that Klein expresses herself.

From her associates, the following fragmentary comments are taken: The Oedipus complex (i.e. the strong internal self drama) begins in the phase in which active polymorphous signals come from erogenous zones and the child fluctuates between one erotic desire and another, and also between pleasurable and destructive aims. (Why destructive is not yet clear). The parent frustrates his desires, as well as destructive components of the child's cruel cravings expressed both external and internal. (Its finally dawns on the authors that the Freudians really mean the sadistic component. Thus one must add to the initial command, "Don't just mush it around in your mouth, bite on it!"). First the oral impulses lead in the orchestra, then the urethral and anal, and finally genital excitations are linked with pre-genital fantasies. In the <u>second six months</u> the genital stirrings gain in strength. There can be rival hatred and jealousy of a sibling, and a desire for a baby. In this early phase are the origins of the unconscious equation of breast, penis, feces, child, etc. and infantile sexuality which Freud attributed to 3-5 years.

One certain observation is that the infant does physiological things like breathing, sucking milk, excreting, moving about, sleeping. These are 'pleasant' activities. If activities are frustrated, the infant becomes 'angry', generally with the anger first shown in the situation in which the frustration lies; he will breathe, or suck angrily, etc. The early aspect of these pleasant and angry activities is interchange from inner to outer worlds. Slowly a view of 'people' forms, as a more whole concept developed out of parts, memories, and associations 'good' and 'bad' have to do with satisfying experiences, and frustrating experiences in both the inner and outer world. The integration finally takes place that the 'good' and 'bad' part coalesce into a single image of the same object. Out of this arises the ambivalent reaction of both loving and hating the same object, that the same object or 'person' can lead to gratifying or frustrating experience, and that in here can arise an origin for depression - of guilt, remorse, regret, etc. The superego arises as an elaborate, inhibiting, stimulating unconscious construct to deal with these problems of love and hate and depression. "Regardless of how old the person is, if he has not dealt successfully with the infantile depressive situation he will be left throughout life with an infantile attitude to the dangers of realizing that he is a being who can both love and hate simultaneously and can feel simultaneously both feelings for the same person" (Scott, p.45).

(At this point, the problem of 'mind' for a physical view begins to loom into perspective.

a. The brain is 'obviously' a computer. This is borne out by the essential play-acting role of transforming input information into keys for action.

b. The brain program 'obviously' develops into a complex algorithmic program for transforming input in space-time to an output posture in space-time for the bodily system.

c. The transform is not a simple transform that would fit an elementary description of 'mechanistic', or 'automatic', or a simple mathematical operator. Instead it is a complex time varying, space varying code 'book' that loosely, but consistently transforms input into output.

d. <u>As a first approximation</u>, regardless of how complex the algorithm is, it <u>has a very simple aim</u>, the dichotomy of to be attracted or not to be attracted, to lock into temporary space-time orbit, or not to lock into space-time orbit. This requires some explanation.

In physics, there are two general sources of 'force', philosophically recognized; forces that act at a distance, such as gravity, electrical, or magnetic forces - at the moment it will be useful to skip relativity; and the interaction of dynamic systems, which at the scale of observation, disregard certain exchanges that take place by sleight-of-hand on a smaller and more rapid time scale and become the equivalent of exchange 'forces'. These exchanges give rise, in one context or another, to transport coefficients of viscosity, etc. which thus resemble interacting forces. The neutrino, the source of gravitational force, nuclear forces, etc. are problem areas in current flux physically.

The biological system similarly interacts. Its signalling in and out of

the near 0.1 second scale, i.e. the reflex arcs, the involvement of sensory and motor elements, represents a foundation for such a binding interacting exchange system. Out of this complex, and the highly complex maturing algorithm - the superego if you will, as a name for the 'construct' - the basic decision making logical structure arise, to be attracted or not to be attracted. Shall we tarry a few moments with this blend? Shall we eat? Shall we run? Shall we read, talk, think, etc? Time element by time element, the biological system plays out its play-acting role by these decisions.

e. The Freudian contribution, this algorithmic structure forms when young, was not there in very complete form at birth, requires a 'plastic', or 'adaptive' structure, the 'cortex' for its development, and is created out of the fibers of infantile satisfactions and frustrations).

The childhood content of play experience as involving Freudian elements of the 'good' and 'bad' breast, the penis, feces, urine, inside-the-body, and outside-of-the-body orientations, the mouth, the anal region and that they are related to behavior and conduct, to a recognition of self, and other-than-self, to split images of self is well illustrated in an analysis of a 3 year old described by Lois Munro in "Steps in Ego-Integration Observed in a Play-Analysis".

(There is little doubt that the ego is presented as an integration of the entire view of self, as all parts - internal signalling, external signalling - are identified as convenient wholes and segregated, as a working hypothesis, into a variety of compartments. It is not inconvenient to regard this as utterly essentially and identified as the 'cortical' complex as a whole in which function has been 'temporarily' at least frozen into structure. If there are schools that disagree with an ego theory, it doesn't really matter. They have to come up with an integrative view that the system takes anyway.).

The following "Analysis of a Three Year Old Mute Schizophrenic" by Rodrigue is an interesting example of communication with a biological aystem, a child, in an 'autistic' state (i.e. in a similar unverbal state that Sullivan has also described as 'autistic'). Furthermore the likelihood of physiological connection with the emotional condition seems to be chronologically documented. "...deterioration of his condition had set in only about the middle of his second year, the basic problem.... could be traced back to his first months of life. ...physical and intellectual development did not grossly deviate... until after he was sixteen months old." From a marked indifference, through a gradually growing play interaction with toys the analyst was able to trace the rigid scheme of his controlling fantasies. There were, or there appeared, all sorts of behavior flashes that did not fit in with the general autistic pattern. Hallucinatory response also made themselves evident. This, and a response interpreted as a capability to experience active persecution were cited as evidences of a growing coherence in the child's ego during treatment. More systematic studies by Kanner in his book CHILD PSYCHIATRY is referenced. In general these children are viewed as narcissistic, tied up in an inner world fantasy. (Certainly the reality of internal drama comes out of such studies, and its out-of-focus quality with regard to 'norms' in human behavior. The issue is not the question of 'norms' but what it reveals regarding possible connections internal to external. Furthermore, one continues to get, over and over again, the impression that it takes a few hundred sessions of the analyst to get the logic of the structure of the individual's algorithm into mind).

In another analysis by Rosenfeld, the extrenal playacting of fantasies that are representative of the superego are discussed. He believes that it is much easier to get an insight into the early infantile processes in an acute regressed schizophrenic.

The following structure of ideas is abstracted from a chapter by Bion. Starting from Freud's simple formula "Neurosis is the result of a conflict between the ego and its id, whereas psychosis is the analagous outcome of a similar disturbance in the relation between the ego and its environment..", and the reality principle (Freud's 1911 "Formulations regarding the Two Principles in Mental Functioning") in which an increased significance during a psychotic maturation becomes attached to external reality and the heightened 'significance' of sensory qualities in addition to internal pleasure and pain which previously engrossed the organism, establishes the (non-linear instability) depressive position Here the organism makes destructive attacks on his total 'personality', the 'ego' that is concerned with establishing internal and external contact. These 'ego' aspects, Freud cites as 'attention', 'notation', 'impartial passing of judgment', a new function concerned with action which previously led to motor discharge, and restraint of action. These qualities are those that permit increased tension without requiring immediate discharge. Bion, in particular, regards all of these involved ego aspects, as being aspects also involved in the development of verbal thought as the essential festure of these ego functions. There is a psychotic 'castration' of the ego in the consciousness attached to the sense organs. (It is impossible to read the work of good students of Freud without continually being impressed by the general underlying computer logic. This makes no claim for the validity or non-validity of the concepts, only for their topological significance. Here, for example, the revolutionary nuance, is laid down that verbal thought - not necessarily external 'language' - but the internal language is the actual internal communications element by which the running algorithm of the system is organized!) Bion cites Klein's 1930 paper "The Importance of Symbol-Formation in the Development of the Ego" as a source for this idea.

The reality of tension in the patient seems quite real, and Bion argues out the case to what extent the analysist's fantasies are projected in the situation. Nevertheless there still remains a very positive role for the analysis program.

The schizophrenic uses language as a mode of action, as a method of communication, and as a mode of thought. These are illustrated.

In paranoid states, Paul Heimann indicates that the patients derive a good deal of sadistic gratification in dwelling on their sufferings. This provides a defense and some support for the ego.

It is quite clear to her that internal interjection (introjection) of the analyst into the patient takes place, so important a part of the therapeutic process that Strachey, linking ideas with Klein, defined it as a means by which the infantile 'archaic' superego is modified and becomes more realistic.

Introjection occurs from the beginning of life, starting from the two aspects, gratifying and frustrating, of the first introjected object, the mother's breast, or substitute. As more and more is introjected, the ego and superego develop in interacting fashion.

Whereas introjection becomes connected with depression, and is specific for depressive states, the same mechanism of introjection in paranoid states does not lead to guilt and depression. (However, there is no concern at present at being amateur psychiatrists, so that the psycho-pathology states are dropped at this time, except for one catch-phrase comment). Freud well-summarized the state as "The person who is now hated and feared as the persecutor was at one time loved and honoured". The paranoid shows introjection, ego splitting, intra-and outward - projection all set in motion against a persecutor.

There is a warning note in a chapter by Thorner, who makes Jones' point from "The Theory of Symbolism" that the development of abstract thinking from concrete thinking is not the same as symbol-formation. A psycho-analytic symbol, presumably in the infantile mind, is a concrete object representing another primary object. In schizophrenia there is difficulty in using or forming symbols.

There is a second section on applied psa. It opens with a second chapter by Klein "On Identification". Identification is a normal developmental signal to introjection. The superego, illustratively, is the introjection of the father and the identification with him. In her own summary, superego traces back to introjection in earliest infancy stages; primal internalized objects form the basis for complex identification process; persecutory anxiety, arising from birth experience, is the first anxiety form, followed soon by depressive anxiety; introjection and projection operate and interact from the beginning. This interaction both builds the external world and shapes the picture of external reality. The inner world consists of objects, first the mother, internalized in various aspects and situations. The relationships between the figures and the ego, are experienced - when persecutory anxiety is dominant - as mainly hostile and dangerous; they are found good and loving when the infant is gratified. Thus while the infant is profoundly influenced by good and bad external experiences, he influences his perceptions of the external world in a decisive developmental way.

(The system's 'aims' are directed at simple ends, to act or not to act. Now one must add the instantaneous view of the world as being determined in part, whether the system is receiving in a 'gratified' state, or in an 'anxious' state. Here arises a case for the time variant responses.).

The infant shows sadistic fantasies against the mother. It experiences fantasies of entering the mother's body, in attacking, in putting excrements into her body. Parts of the body are split off, projected. This soon extends to the father and other people. In her view, paranoia and schizophrenia develop from the persecutory anxiety and fear of retaliation resulting from oral -, urethral - and anal-sadistic impulses. Identification of certain projective mechanisms, which are complementary to these introjective ones, develop. These identifications form part of the paranoid-schizoid position during the first 3-4 months of life. The ego is largely unintegrated and may belikely to split itself. In normal development, in the second quarter of the first year, persecutory anxiety diminishes and depressive anxiety comes to the fore, as a result of the ego's greater capacity to integrate itself. Internalized images, the good breast, acts as a focal point in the ego; it counteracts splitting, and enhances ego-integration. However, the breast taken in hatred is the prototype of the bad internal object, and a primal source of splitting in the libido theory, such internalized images, here the

good breast, becomes endowed (cathected) with libido (i.e. discharges of 'libidinous' or gratifying nervous impulses, that is the equivalent of 'gratifying' signals on the level of the 'hypothalamus'. The content of Melanie Klein's ideas is to build up a theoretic structure on Freudian lines for the infant. One will have to remember, in viewing any criticism of this structure, that it will have to be built on clinical data as carefully sought after as Klein's and her colleagues. One may not dismiss it with light logic.)

In a following chapter, Joan Riviere attempts a quieting interpretation of the inner world, which starts from Freud's recognition that objects are internally injected (introjected) and leads to the mental complex of superego. However there is a difference between the superego, modelled mildly on parents personality; and the primitive and fantastic 'personal relations' we have with the figures who people our inner worlds. The 'inner world' concept is resisted. It is not understood, and it is anxiously rejected emotionally.

Besides having explored this theme in earliest childhood, Klein is also responsible for stressing an almost obvious platitude, the life of the emotions continuously active in us is based on a simple pattern; everything in it is either good or bad, nothing neutral. Good inner world objects tend to be taken for granted. The bad are involved with anxiety. This is also true when the internal objects are people. To the infant in particular, in whom life is governed by pleasure and pain (should this now more generally be anxiety?) both his own feelings and his objects are either pleasurable or painful (anxiety). It is particularly characteristic that his own painful sensations are projected internally and attributed to parts that are not-him. In a poetic example, there is the wish to encompass the loved one, but a fear of the loss, and a craving for possession of something outside oneself. "Food would be the evident prototype of such a desire and need...primordial human phantasy belongs of course to the order of instinctual impulses classed as cannibalistic... through Melanie Klein's work... understand... common... origin of... unrelated human experiences of incorporation... and ...cannibalistic acts... undeniable link... in the intensity of sexual passion to incorporate the loved one... devouring with the eyes... is commonest... activities between lovers", finally "The fear of loss is a dynamic factor in the need to possess and incorporate". While Freud had put the source of the fundamental fear and anxiety on the leve of genital loss or envy, Klein finally placed it at the level of fear of the loss of life itself. "We cannot escape the conclusion that an intense fear of dying by active agression or passive neglect is a fundamental element in our emotional life, is as deeply-rooted in our unconscious minds as life itself and is barricaded off from conscious experience by every known mechanism of defense", i.e. beyond anxiety there is terror. In this complex personality that is the human's, this anxiety and fervor binds human to human so intimately that all of us are "members one of another". While all theoretically well-known and obvious to any analyst, it is not appreciated sufficiently emotionally. Instead the fiction is clung to of absolute individuality. The person is basically bound together by memories.

(There is little doubt that the psychoanalysts, particularly Freudian, have uncovered the 'inner world'. Whether they have done so accurately is another matter. However this is not a quarrel on principle but in what will later on prove to be scientific details.

The structure of the brain must be one such that the system can deal

automatically and locally with closed loop local balancing, and regulating chains with some central input to sense the state of its far flung empire of mechanisms; at a lower level of the brain it must be able to deal automatically with inter mechanism conflicts by programming a wide series of interconnected regulating chains, here the input of sensed information is much more copiously available to the higher control centers - it is not inappropriate to consider this structure and flux of information as representing the "es" of the system - the higher center programming is not completely determined, it is sketchily laid out at the beginning, it is an adaptive control program. What begins to appear is that there are a few counterdriving response elements that the brain is capable of making. If we were developing physics in the Newtonian program, we would say that a system continues its state of motion $\dot{X} = 0$ unless acted on by a force. Force is what changes the state of motion. In particularly it changes it by

$$F = m\ddot{X}$$

F = affecting force
m = a property of the system - inertial mass
$\ddot{X}$ = acceleration, which characterizes the state of motion of the system.

Similarly, but only analagously, these response elements might be referred to as 'forces' or 'drives'. These are not operationally defined at present, and as a result do not make a physicist happy. However 'gene' was also not originally defined, or 'atom', etc. They were useful hypothetical concepts until a structure and mechanistically determined functions could be demonstrated. Thus the 'driving' elements in the brain are to seek gratification, i.e. to choose courses of action by the internally 'self-actuated' motor elements that will set up some 'satisfactory' pattern of signalling into or within the system. What these patterns are, or their centers are is not known. The general vague neurological idea is to put out neural 'fires', a most appropriate pun, and one perhaps worthy of Freudian investigation. One can get the idea - at least for some people - that warmth is more 'gratifying' than cold; cool than extremely hot; eating than hunger; mild hunger than overeating; mild exercise than tremendous exertion; mild challenge in the environment than passive satisfaction, etc. The list is indicative that extremes of effort are not that gratifying, and that in any context there is a more central tendency in the range of human motor capability that is more gratifying. The object of this idea is not to produce the picture that the 'drives' are 'central forces', in a physical sense, that restore the motion, but that they do seem to be preferred states within the scope of the individual's motor abilities, and that they do have the desired Freudian and even behavioristic end of pushing the system into an ever seeking path. It also represents part of the requirement for locking in of space-time orbits. The pain part of the pleasure-pain principle has not come into focus before. It is becoming clarified in viewing M. Klein's work, and later H. S. Sullivan that the second 'drive' is 'anxiety', not as the opposite end of a dualistic spring force with pleasure at one end, and pain at another. If the dichotomous state picture is accepted it would almost appear that there were two independent acceptance systems, the gratification system, and the anxiety system, and that by an exclusion principle, either one or the other dominated the inner world at any instant. This modelling of bistable states can easily make the shaping drives of behavior a weak non-linear limit cycle oscillator operating between the states of anxiety and gratification. The stability is determined by the total sensed input information, namely by the flow of information from the "es" or id. Thus once more the logic is

inverted. It is not the cortex which puts out the fires of the hypothalamus, but the fires of the hypothalamus heat up the unstable structure of the cortex, and as a fed back resultant has its fires quenched!!

Now there is an even more imperative driving system than anxiety. This appears to be a terror system. In the terror state, all motor units are alerted to operate drastically. Whether this is an independent system from the anxiety system is not known.

Thus what is being here premised is that the primitive logical acceptance systems involve a gratified state, an anxious state, or a terrified state. The gratified state and anxious state form a bistable oscillator, which in the face of a 'usual' flow of sensory inputs develops a certain characteristic duty cycle for the individual. Its actions are keyed by whether he is in the gratified state or the anxious state. However, if now, a flux of sensory information comes in that is not so usual, it may affect the stability of the oscillator duty cycle. In one individual this may provoke the anxious state, etc. The characteristic logic by which these sensory inputs affect the fundamental emotional stability oscillator is what makes up the details of the executive logic. The logic of the stability oscillator is simple Boolean, the logic of how the two state system is switched is not. This becomes the complex detailed algorithm that takes information from the 'hypothalamus', that has its own computer banks and sensory data processors, and memory cores in the higher brain, coordinates a view of all this information into a near simple two state switching resultant. What Melanie Klein has forced is that the two state switching logic is developed very early out of very simple 'gratifying' and 'anxiety' content of infantile information. What we derive from this is that the logic develops along with the maturation of signalling from the lower nervous systems in their connections toward the more central nervous system, and also that the communications elements must be near 'verbal', i.e. either mechanical or electromechanical pulsed complexes, spaced out in time).

Two subsequent chapters by Segal, and Stokes on psychoanalytic constructs for art are interesting, but tangential at the moment. The next chapter by Money-Kyrle is absolutely brilliant in its simple logical pursuit from philosophy to science to psa to the ethics of human conduct, and to its bearing on social-political problems, but unfortunately it is also tangential. A beginning structure for social system is very interestingly discussed by E. Jaques with some very thought provoking discussion about the formation of institutional groups within society, but is also far afield. (The only tentative inference that we can permit ourselves is that the philosophic structure of science laid down in (58) stands up quite amply in very detailed scrutiny in many fields; here in the consequences of psa theory).

Views of H. S. Sullivan

The flavor of Sullivan's ideas were sought in (59), based on a lecture series of his conceptions of psychiatry. As Cohen's introduction points out, Sullivan was interested in the study of interpersonal communication. The underlying psychiatric propositions are that mental disorders result from inadequate communication, which is interfered with by anxiety; persons are involved in an interpersonal field rather than as separate entities.

Basically, Sullivan began as a Freudian student, and has developed in his own directions, mainly in neglecting infantile sexual behavior and detailed hysterical processes, and emphasizing interpersonal interaction. He attempts to conceptualize the dynamics of interaction in the infant and mother, with three modes of experience - prototaxic, parataxic, and syntaxic. The critical divisions are based on the crucial role of language in experience. Prototaxic is before symbols are used; parataxic refers to experience in which private or autistic symbols are used; syntaxic is used for communicable experience involving common symbols. Sullivan contributed the concept of dynamicisms as "the relatively enduring patterns of energy transformation which recurrently characterize the interpersonal relations... which make up the distinctively human sort of a being". (A relatively time enduring pattern of recurrent energy transformation defines an oscillator complex. The idea that this, in interperson relations, makes the particular human distinct states that each person has a particular complex of internal oscillators, with regard to their interperson relations. Thus the fundamental thesis being gradually developed in this program at every level of biological phenomena, here the interpersonal behavioral relation, continues to grow and find support from the marks of biological masters, such as here from Sullivan).

The interpersonal field is made up of interaction of a variety of dynamisms of two or more organisms. Some dynamisms integrate the situation; others involving anxiety lead to disintegration. Anxiety is the chief disruptive force in interpersonal relations, and in the development of serious difficulties in living. Anxiety is only defined 'operationally' in terms of effects. The question of how anxiety is communicated from mother to child is unanswered by Sullivan. In his psychiatric treatment, Sullivan always posed himself one question. "Where is the flow of communication being interfered with by the threat of anxiety?" His basic assumption regarding human behavior is that it is positively oriented toward collaboration and mutual satisfaction and security, unless interfered with by anxiety.

In briefest outline of his ideas, Sullivan mentions:

As part of things we catch on as infants, there is a capacity in every human being to experience anxiety. Anxiety is called up in the interpersonal relationship between infant and the person with whom the infant is doing something, classically in a disturbance of feeding. The fearful state is provoked in two circumstances, violent disturbance of contact with ambient reality, and disturbance in the mothering one. There appears to be a primitive (more primitive?) anxiety that arouses uncanny emotion. (These ideas are increasing validation for the concept of anxiety and terror as condition-states).

Psychiatry is the study of interpersonal relationships. Man has a deferred childhood; with abilities maturing slowly and serially and quite labile over 10-20 years, utterly dependent at birth, and quite dependent on tender cooperation of the human environment 5-6 years after. The moderate personality differences that exist from person to person arise from physical differences in such things as sensory sensitivity, comprehension ability, rates of maturation, and language. Out of experience arises the perception of the outer world. (According to Sullivan, the infant perception starts with momentary states, later identified as before and after).

Experience occurs in three modes, the prototaxic, parataxic, and syntaxic, which are primarily matters of inner elaboration of events. The prototaxic mode, the probably basis for sentience, is the discrete series of momentary states, with special reference to the sensitive sensory states "it is as if everything that is sensitive and centrally represented were an indelible, but very greatly abundant, luminous switchboard, and the pattern of light which would show on that switchboard in any discrete experience is the basic prototaxic experience itself".

(Fine! We are quite encouraged. The beginning of thinking is the projection by which the system state - from the hypothalamus, from direct senses,- are projected up into the higher brain, for possible computer control action. The most primitive experimental mode is momentary and fragmentary - 'non-symbolic').

The background biological premises are: communal existence, the living cannot live separated from their necessary environment, as illustrated in physico-chemical contact; the principle of organization, biological systems are organized; the principle of functional activity, a complex of physiological functions are suitably interconnected for functional organization. The stages of development are infancy from birth to articulate speech; childhood from articulate speech to the need for peer playmates; juvenile era through 6-12 year range until a maturation need grows for intimate relationship with a 'chum', with comparable status; preadolescence which extends until genital sexuality and puberty erupts, or really with change of interest from own sex to a person of opposite sex; adolescence which in this culture continues to a lust and genital drive satisfying pattern; late adolescence an era in which some other developed aspects of personality fall into place; adulthood involving relationships involving love for another person as significant as one's self.

Two opposing states of the system are euphorial (satisfaction, gratification), and tension (anxiety). Tension may be developed by needs, and may develop overt or covert energy transformations with a relaxing toward euphoria with its satisfaction. The observed activity, resulting from infantile tension needs, induces tension in the mothering one, which is experienced as tenderness and an impulse to activities that relieve the infant's needs. (One must realize that at this point, the Freudian system, etc. break down. They supply no mechanism for the coupling. Dr. Rioch in conversation a few years ago, objected to the trite statement of 'hormones' as the activating mechanism. Yet Sullivan's "need for tenderness" is no better. It appears clear, even with (55) which still describes a fairly rare occurence, that females are 'attracted' to infants, that 'warm' 'tender' feelings, obviously chemical, greet their view of a child. However the argument is certainly weak on everyone's part why the mothering person, whether human or otherwise, is willing to devote so much 'unselfish' effort to the infant).

The tension of anxiety in the mothering one, induces anxiety in the infant. In the infant, the floating nature of experience makes the tension prototaxic, whereas in adulthood the verbal content.."hunger" in its more complex syntaxic mode offers a much larger capacity of action for relief of the anxiety. The infantile anxiety illustrates that anxiety is not specific, it is not manageable, it is induced from another person. In infancy, the first danger is from anoxia and is accompanied by the form of fear known

as terror; Such extreme starvations - oxygen, water, freezing, etc. - invoke the felt aspect of tension from fear to its worst form of terror. One may deal with fear, in adulthood, by destroying, escaping from neutralizing, or ignoring the situation. In primitive way, the motor responses of infant deal with the tension situation, in related fashions, with the cry as the most effective infantile behavior appropriate to the relief of fear. (The whole loop is not accounted for, except that it invokes an anxiety response from the mother).

In a general vague way, while the infant action in response to need, in developing anxiety, would appear to change the system state to one dangerous to the organism, the infant has a series of dynamisms (organized repetitive activity patterns - 'oscillators') which can intervene and in the anxious terror of a shrieking, kicking infant, apathy intervenes to attenuate the tension, not abolish the need, as if the system in speeding up the response had used up its higher operating level energy and had to retreat to a lower operating level. Other repetitive dynamisms that relieve tension is detachment for prolonged severe anxiety, and sleep.

The infant is endowed with a zone of interaction - the oral zone - as one interface in its communal existence for oxygen, sucking, etc. (One can only feel that Sullivan is developing a smoothed out Freudian view of the system that doesn't call for as many 'theoretical' constructs. However one always feels the parallelism, and near identity). With its sensory receptors, motor effectors, and central "eductor" midprocess in the brain (the abstraction of the process complex in the brain) it is the end station for a particular type of generalized communal interface, that has striking psychiatric importance (and presumably structural importance) but also of striking importance for the organism as a whole. (One cannot feel much difference between this and the Freudian oral -, anal -, urethral - concepts. This is no criticism. It simply suggests,that to some extent the response complex is arrayed in a bank. This will be checked out in the future against Penfield's explorations).

As a result of repetition, the crying-when-hungry, crying-when-cold, crying-when-pained, etc. reactions of the infant, each distinct, each develop, as if with 'magical potency', a satisfying response in prototaxic terms from the mothering one, and begins a development and differentiation of experience. The situation complicated by anxiety, in which a desirable resultant does not occur, requires development of adequate ways of handling such experiences, and begin to shape the dynamisms of the individual - in the infant, such as alternation of anxiety and apathy. The mother's anxieties are just as shaping of experience. Although anxiety is a total experience, it may become erroneously associated with particular zones of interaction.

With developing dynamisms, the infant moves out of the prototaxic mode and into the parataxic mode of experience where the experiences begin to have symbolic value - the nipple becomes "a sign that satisfaction of hunger will follow except when crying has evoked the evil or bad nipple with its aura of anxiety"; (Thus, here is evidence that the proposal of an alternation of the overall state is not an idle speculation but also lies within the scope of Sullivan's scheme. The following details may be added. In Sullivan's views, one would say that the oscillators, or rather, the

integration of the central nervous systems view of the gross system oscillators begins to develop within the scope of the parataxic mode as signalling ' 'symbolic' complexes develop, and that the system as a whole then switches from an anticipatory satisfaction state to an anxiety state. An added detail , one surmises, is that whereas at the beginning of the 'parataxic' mode it is a simple 'sign' or 'symbol', the nipple, etc., that pushes the infant over into an anticipatory state, or crying, etc. into an anxious state, as the almost periodic 'mood', or 'mode' relaxation oscillator develops, it is not a simple symbol that pushes the adult state over, but a large complex of inputs.).

The primitive perceptions, with its signed meaning makes up the rapidly differentiating prototaxic experience. The experimental encounters include the good-and-satisfactory uncomplicated signal the good-but-unsatisfactory signal which is only acceptable when the 'hunger' is great enough; the wrong-signal which is rejected and leads to further search; and the evil signal which is preceded and accompanied by anxiety. The first three are encountered predominantly orally but sensory in the infant, the fourth is evoked from original oral zone interaction but with no sensory source. In a vague sense, there is possible a 'somatic' organization correlating related structures with psychiatric phenomena (an example of possible afferent thumbs and lips connections is given).

The infant eventually progresses to recognition of a complex pattern of several zones of interaction, and in such complexes lies the parataxic mode, such as the complex of experience of the good mother, or the bad mother. Differentiation of complexes depends on more subtle clues, such as cues - forbidden gestures are an example -, and indices; the organism in which things are signs is an 'interpreter'. The 'interpreter' is the active system which transforms a body of physical phenomena into a 'personality'. (Here is Sullivan's statement that really contains at its foundation the need for a complex computer algorithm that will organize programs of interpretation rather than simple computational acts or complexes).

It is essential to recognize that there is no 'visual' difference between the good state and the bad external state, yet it may invoke completely different responses. Viewed overall, "the satisfaction of a need is the ceasing of an integrating tendency to manifest itself in work", which as energy transformation in functional activity is one of the fundamental aspects of all living (i.e. the system is self-operative for seeking out gratifying ends). The anxieties of need integratively tend to drive toward the goals of satisfying hungers by activity. The recurrent tensions or anxieties, are analogous to physical conversions of potential and kinetic energy, in their conversions (i.e. are oscillatory). The living cells, the systems, the organism as a whole, even the entire world, and the organism connected to its ambient milieu are organized as dynamisms " "the relatively enduring pattern of energy transformations which recurrently characterize the organism in its duration as a living organism". (It is no loose statement that Sullivan, twenty years earlier, is obviously stating the thesis that the biological system is made up of an oscillator complex. The added element, which he of course also anticipated, was that the oscillator complex extends to the relation to the environment and interpersonal relations. The latter, we have 'discovered' in orbital synchrony, and the former, we are in process of determining as we inter-

relate organism and its passing in and out fluxes. Thus these beliefs, backed now by ever increasing biological and psychological authority, cannot be dismissed lightly as they touch base ever increasingly with the older masters. One must continue to recall that such a process is a necessary ingredient to lend credence to the physical modelling of events. We are not trying to rediscover 'sex', as it were, but to 'explain' its physical nature).

A pattern, as definition, is an envelop of the 'insignificant' particular differences which preserves the essential character of the form. In the organisms, experience is marked by many recurrent patterns involving significant energy transformations (one may recall that in (1), the study goal was directed only to those oscillator patterns that involved significant physical energy or communications energy content. It is quite clear that Sullivan would have favored these goals quite highly).

The dynamisms of particular interest to psychiatry are of two categories: those conceived of with regard to recurring tensions or anxieties which recurrently disturb euphoria in the organism and show themselves in interpersonal relations as particular integrating, divisive, or isolative tendencies; those conceived of on the basis of energy-transformation characteristics of particular zones of interaction.

"Personality is the relatively enduring pattern of recurrent interpersonal situations which characterize a human life."

The infant's 'personification' is not the real mother but an elaborate organization of the infant's experience. Persons other than the mother may have great early influence as surrogates. Beside the possibility of tenderness, the mothering one or surrogate may show malevolence as well as anxiety. Nursing is most often nearly the first organizing experience.

The interacting zones, often themselves dynamisms (oscillators) invoke zonal needs. Thus there may be a need to suck, etc. and a s one basic research (60) on pecking of chickens indicated, if obtaining food was easy, chickens would peck away at each other to discharge the energy associated with the zonal need (that the maturing nervous system should not invoke high impulse to discharge energy in practicing would be quite surprising).

The end zones - anal - and urethral -, for expelling food residue and excess water develop tensions of central importance. The complete separation is of great importance for theory, requiring as it does tender mothering cooperation, and is thus much more interpersonal.

The developing dynamism associated with the overall oral zone is marked by Activities which may uncertainly be called 'pleasurable'.

By six months the infant is involved in a variety of interzonal needs and some related sign processes, and considerable maturation has taken place, so that two or more zones may be coordinated. In particular manual-oral coordination begins a differentiation of the infant's body from the rest of the environment.

(This is of course a basic point. Whether it strictly stems from manual-oral coordination or not, it certainly is clear that the signalling from two

or more sources must be the foundation for 'directionality', such as in the ear, or eye, or hands, etc. Thus if the bilateral symmetry of the body is imprinted in the 'cortex', it is similarly clear that different zones or regions are also imprinted in the cortex. The important thing is that topologically there is a one-to-one correspondence between interfacial zones of interaction and regions in the cortex, not that they are fixed, but that even if disturbed or eliminated, they will be reformed in some fashion. Thus interfacial 'reality' becomes marked on the cortex and is the representation of 'reality'. Here the basic point finally emerges that 'orientation' or differentiation of 'direction' begins to result when two or more more-or-less 'permanent' interfacial zones begin to throw a signal complex into the cortex. Thus, to coin a physical catch-phrase, 'reality' is marked in the cortex as a nonmetric slowly time-varying 'tensor' orientation. The tensor 'orientations' that are involved are a tremendous number like up-down, before-after, left-right, hands-mouth, eyes-hands, etc. The slowly-time-varying implies that the cortex does not need to have, nor does it have a fixed imprint of outside. It has the additional spatial property, that a signal is marked and fades, but a complex of repetitive signals gradually is marked and 'etched' into the surface, but scattered quite a bit, since each signal likely is noted much more randomly, and it is only the mean complexes that are well sketched out. The property is like that of a long persistence cathode ray screen, which will show a complex of transient lines, but a rather clear persistence of the well tracked areas. One may judge from the learning time of infants and the relearning time of adults who have had patterns shifted that the scale of time persistence of a pattern is in the months domain.

Thus the early oral signal, dominating the cortex, gradually develops some fundamental episodic, dynamism, or elementary oscillator states - since it is so plastic and therefore likely unstable. The rudimentary episodic states seem to involve the gratified and the anxious state. Tensor orientation has no meaning yet particularly, although 'convolution' does, that is detailed sketching out of some time varying patterns are being marked throughout the cortex. As the infant passes a few months of life, the signalling complexes with growing strength in their mean affective energy, i.e. the energies that they can tie up in motor units when their signal has been amplified, now begin to clamor for a role in the cortex. The slowly 'convoluting' cortex must turn its localization over, contract it, and make room for the newer zonal system signals. Topologically, the episodic, fragmentary nature of signalling gives way to a spatially and temporally bound command logic that controls motor units connected with interzonal interfaces. The interfaces can be advanced or withdrawn, etc. The overall control logic remains similar. What are the motor adjustments, in response to conflicting signalling complexes, which will switch on the gratified state as compared to the anxious state? Viewed as a two state color analogy, if the gratified state is white, and the anxious state is purple, there is a gradual switching from one color state to the other, both in time, as a limit cycle, and due to existing clamour, as a relaxation oscillator.

As the logic begins to deal interzonally, Sullivan says, nature says it shall be invested with symbolic content. Why is not yet clear. It is not clear in animals. One is perfectly willing to accept the idea that a signalling abstraction is needed to represent and be able to equate complexes from competing systems, i.e. the problem exists of defining existence of signal, quantification or measure of signal, non-evanescence of signal, permanence of

signal, equality of signal, greater or less than of signal, additivity of signal, temporal order of signal, etc. One is willing to accept that a 'machine language' is needed. This is likely up to Sullivan's parataxic mode. The reason for a syntaxic mode is what is not so clear at this time).

The six month infant is well advanced in a beginning toward oral-manuel sentience and manipulation, furnishing the point of departure of a considerable formulation of his body, of self-sentient knowledge (the mouth of thumb, etc.) and sentient knowledge of the non-self. Body exploration is often interfered with, in each society often in specific ways, and represents a large source of communication of anxiety from the mothering one to the child.

By mid-infancy, 6-8 months, from mothering contacts, the infant learns postured patterns for the face as a cue source, and also trial and error sound complexes - phonemes.

Thus learning begins from its connection with anxiety - one doesn't learn from anxiety but it changes the state, and from discrimination of the gradient (derivative) of anxiety, i.e. its increasing or decreasing rate.

A technique of sublimation is adopted in not very many months of age in which a partial satisfaction of a need will be accepted in lieu of a complete satisfactory activity.

(This demonstrates the non-linearity of the system, as did the adoption of the cortical zones to make room for conflicting signalling complexes. In both cases, an instability causes a switch over from one state to another without a full linearly connected passage from one state to another; it is sufficient that anxiety has been lessened, by a comparison symbolically of anxiety value, to non-linearly switch over and 'sublimate').

The next most important learning process is trial and success to relieve anxiety - the mothering one commonly uses rewards and punishments.

(It is in this complex that the roots of attractive 'forces' and orbital synchrony begins. The 'attractive' forces act to lock in on successes, and 'repel' from failures).

"Three aspects of interpersonal cooperation which are necessary for the infant's survival, and which dictate learning" are rewarding, grading of anxiety and severe'uncanny' anxiety.

(Thus the Sullivan dicta lead here to the same ideas that we have managed to call out, from our own thinking, from Freud, from Klein, and now from Sullivan. The drives to learned behavior are gratifications, anxieties, and a super-anxiety which we called terror, and which in any case Sullivan better identified as 'uncanny'emotions).

The personification begins of good-me, bad-me, and not-me, as the beginnings of the self-system, as the 'introjection' of the mothering image. (i.e. as the cortical complex begins to topologically organize into an orientation that resembles what is communicated from the mothering one. All of this begins to fit a primitive view of the brain, the systems differentiation of the body, the inputs from the external environment, the mothering interpreter that

helps to manipulate the external environment input. It is clear that the infant might learn about the environment by himself - if he survives - because the physical environment is generally consistent in its inputs. Up remains up in an earth's gravity field, night alternates with day, etc. This consistent unfolding must become patterned into the cortex, but the order of learning may be poor. The mothering one presents the order, helps the motor responses, etc. so that a rather uniformly taught product results. It is quite obvious that the experiments with drastic environmental changes will become significant for this study, but not now. The more immediate task will be learning and attempting to match clues in neuroanatomy and neurophysiology).

The dynamism of the self system begins to develop as an explanatory conception "it is not a thing, a region, or what not, such as superegos, egos, ids, and so on" although "there is some noticeable relationship, perhaps in the realm of cousins or closer". (As a digression, our good friends are anti-Freudian. We claim to be neither Freudian or anti-Freudian, only poor-but-honest working physical scientists. Yet we are forced to point out that the Freudian ideas have obviously such primacy and merit that it is foolish to deny them. One can pick and choose, polish, correct, accept, and reject in part and modify, but not reject out of hand. Some pupils may have formed a cult, and Freud's personality is an irrelevant issue. What is pertinent is that it is naive to accept a field of ideas and not be willing to put on a fitting real structure. This, one must note, will always be the physical scientists theme. If you don't know how to build structures, ask the physical scientist, not proposed in snobbery, <u>but because building physical structure is his business</u>).

The self dynamism (the self oscillator complex) begins when there is only the rudimentary personification of good-me, bad-me, and not-me. (In our view the ego imprint, in the cortex, of the growing command algorithm switching from gratified to anxious, and decision making about the recognized semi-permanent interfacial zonal signalling complexes.).

One of the important elements in the signal accepting system complex is selective inattention, the disregard of things that the system is powerless to change; and incongruous distortions that may be introduced, such as from the mother. (If true, don't these also lead to the central mechanism that Freud called repression).

The socialization process of the infant is marked by frequency and consistency of organized experience, and the sanity (temporal-logical organization) of the educational effort.

There is, of course, considerable non-sense demands put on the twelve-fifteen month old child, such as don't grow up, keep clean and dry, don't tinker with the genitals, etc., i.e. there is a growing parental expectation.

A considerable amount of interpersonal relations is represented as covert processes as well as overt processes, growing with the child's ability to delay behavior. (As the system finds ways of resolving tensions, and falls into the qualified state and anxious state pattern, the implied non-linearity does not require immediate corrective action. The system has the ability to time delay actions).

The end of infancy and threshhold of childhood is marked by a covert

operation continuing symbolically and internally in the mind, but disconnected from the action. (The cortex has declutched the motor system, and plays the action out in an unconscious 'memory' bank).

From the end of the first year, the important overt elements of gesture and language begin to be acquired in considerable amount. In the eighth-ninth month, the structure of phonemes, tones, thythms, etc. begins to develop, marked by parental awards or indifferences. The infant's language is at this time autistic (a primary unaccultured symbol activity). By accident there is some verbal identifications, so that the infant is beginning experience in the syntaxic mode - a beginning of leaning forward the communicative behavior of gesture and speech.

In the 12-18 month era, a reverie process, an autistic 'baby' language, begins and is used throughout life, switching from overt to covert, for internal communication, with a nonverbal content.

This brings Sullivan's material up to childhood. While his discussion beyond has considerable signigicance, some of his major organizing points, outside of psychiatric treatment, have already been laid. Since time has run out, the discussion can be here halted and taken up in some future time.

With regard to the content of Sullivan's ideas, once again we find an empathy and little basic diversity with the key ideas of Freud, Darwin, Pavlov, Klein, Sullivan and Hull; that the key ideas are very helpful and in agreement with keying physical ideas about the biological system in general and the behavioral system in particular. We believe, for example, that we have given a fairer summary and interpretation of Sullivan's key ideas than, say, is found in (56) or many other psychiatric and psychological interpretive studies.

Other works which will be viewed in the future will be Horney (61); Alexander (62); and Arieti (63).

Subsequent to that, the neurological findings of such masters as Papez, Jasper, Penfield, Rasmussen will be reviewed. Such work has been begun, but the task is going slow ly, and there is no point to discuss it until a more rounded picture has been conceived of.

Still later, an experimental program will be proposed and begun, to demonstrate the physical nature of human response. Actually much of the beginnings of such a program has already been formulated, but it would be too premature to discuss it.

The upshot of the investigation so far has been to tie a physical view of the overall biological system into consistency with the behavioral system, to find hints that the masters in psychiatric and psychological thought have developed ideas that are not at odds with the current physical view, undergoing development, to find hints in these masters on how to develop and extend the model, to begin to find a finite closing in of the structure of physical ideas that will encompass behavior, the nervous system, and the 'mind', to begin to be ready to view the anatomy of the nervous system for ultimate tie-down to mechanisms, and to begin to suspect an experimental program that can probe operational concepts of the system. We are infinitely encouraged at the rate of progress. Whether the biologist sees or will see this degree

of progress is hard to judge. Nevertheless there is physical appeal in the growing proximity to logical - mechanical mechanisms that can be functionally and structurally related.

APPENDIX - TRANSMISSION ATTENUATION CHARACTERISTICS OF THE ARTERIAL SYSTEM

With the previous long, only very primitive introduction to cardiovascular geometry and topology, it is possible to begin the physical analysis.

The transmission line equations, for a uniform tube, are given by (64)

$$Q = -\frac{A}{j\omega\rho_o}\left[1 - \frac{2J_1(hr_o)}{hr_o\, J_o(hr_o)}\right]\frac{\partial p}{\partial x}$$

$$\Gamma^2 = -\frac{\omega^2}{C^2}\left[\frac{1 + \frac{2(\gamma-1)\,J_1(gr_o)}{gr_o\, J_o(gr_o)}}{1 - \frac{2J_1(hr_o)}{hr_o\, J_o(hr_o)}}\right]$$

$$p = \sum a_i\, e^{-\Gamma x + j\omega t}$$

$$gr_o = (1-j)\, r_o\left(\frac{\omega\sigma_o}{2\nu_o}\right)^{1/2} = \frac{(1-j)}{\sqrt{2}}\sqrt{\sigma_o}\, Z^{1/2}$$

$$hr_o = (1-j)\, r_o\left(\frac{\omega}{2\nu_o}\right)^{1/2} = \frac{(1-j)}{\sqrt{2}} Z^{1/2}$$

$$Z = r_o^2\,\frac{\omega}{\nu_o}$$

The first equation is the impedance equation. The second expression gives the propagation constant, defined for linear proportion. (In (1) it was shown that none of the suspected non-linear terms can contribute much of any significance).

Q	=	instantaneous volume flow
D	=	tube diameter (r_o = radius; A - area)
ω	=	natural frequency of driving inputs
ν_o	=	kinematic fluid viscosity
p	=	instantaneous value of pressure (gage)
x	=	distance along tube
$\frac{\partial p}{\partial x}$	=	pressure gradient
Γ	=	complex propagation constant
Z	=	damping factor (= Womerslay's $\sqrt{\alpha}$)
$J_o, 1$	=	Bessel functions
$hr_o\, gr_o$	=	Bessel function arguments
C	=	velocity of propagation

It is desirable to derive an additional relation, which in the elementary case is regarded as 'the equation of continuity'. If

$$\frac{\partial Q}{\partial x} = -B\,\frac{\partial p}{\partial t}$$

Then for each frequency

$$B = \frac{A}{C^2\rho_o}\left[1 + \frac{2(\gamma-1)\,J_1(gr_o)}{gr_o\, J_o(gr_o)}\right]$$

The treatment in (64) extended to gases, liquids, and somewhat elastic thin walls. Thus has applicability to blood vessels. One may view the transformation as follows: The velocity of propagation in a medium may be computed from

$$c^2 = \left(\frac{\partial p}{\partial \rho}\right)_s = \frac{1}{K_s \rho}$$

K_s = adiabatic compressibility

If the compressible changes come from wall elasticity rather than fluid elasticity, one may simply extend the definition so that

$$K = K\,(\text{fluid}) + K\,(\text{wall})$$

i.e. the compressibility of the composite system is the compressibility of the fluid plus the compressibility from the wall. The wall compressibility is

$$\frac{1}{Y}\left(\frac{\partial V}{\partial p}\right) = \frac{D}{ES}$$

Thus

$$c^2 = \frac{1}{\rho K\,(\text{fluid}) + \frac{\rho D}{ES}} = \frac{1}{\frac{1}{c_o^2} + \frac{\rho D}{ES}}$$

$$= \frac{\frac{ES}{D\rho}}{1 + \frac{D\rho}{ES}\,\frac{1}{c_o^2}}$$

c_o = velocity of sound in medium, s = wall thickness, E = Young's modulus.
Thus

$$B = \frac{AD}{ES}\left[1 + \frac{D\rho}{ES}\,\frac{1}{c_o^2}\right]\left[1 + \frac{2(\gamma - 1)\,J_1(gr_o)}{gr_o\,J_o(gr_o)}\right]$$

holds for both gases, liquids, and elastic walls. If now the medium is very stiff (so that its propagation velocity is very high), and the substance is a liquid with a ratio of specific heats very near one, then

$$c^2 = \frac{ES}{D\rho}$$

The Moens-Korteweg propagation velocity
and

$$B = \frac{AD}{ES}$$

so that

$$\frac{\partial Q}{\partial x} = -\left(\frac{AD}{ES}\right)\frac{\partial p}{\partial t}$$

the elementary continuity equation.

It is therefore convenient to transform these now equivalent relations to

$$Q = \frac{-\pi D^4}{128\mu_o}\,\frac{\partial p}{\partial x}\,\frac{1}{F_1}$$

The first factor represents Poiseuille resistance in the tube, and the second factor F takes care of the impedence characteristics in terms of a damping parameter $\bar{z}$ which transforms the regime from overdamped Poiseuille-Rayleigh

flow (see Rayleigh's THEORY OF SOUND) to underdamped 'organ-pipe' flow.

$$\frac{\partial Q}{\partial x} = -\left(\frac{AD}{ES}\right) \frac{\partial p}{\partial t}$$

appears as the equation of continuity (1).

$$\Gamma^2 = \frac{32\, jw\mu_o}{DES} F_1$$

appears as the propagation constant.

$$c^2 = \frac{ES}{D\rho}$$

appears as the propagation velocity.

$$F_1 = \frac{\left(\frac{hr_o}{8}\right)^2}{\frac{2J_1(hr_o)}{(hr_o)\,J_o(hr_o)} - 1}$$

$$hro = (1-j)\, r_o \left(\frac{w}{2\nu_o}\right)^{1/2} = (1-j)\left(\frac{z}{2}\right)^{1/2}$$

$$z = r_o^2 \frac{w}{\nu_o}$$

Consider now a tapered tube which is well endowed with side branches regarded as porous holes. The continuing sum of bleed-off areas is essentially equal to the diminution of area of the tapered tube so as to preserve mean velocity. Because of the topological model of subdivision, it is also true that the reduction in area per unit length (i.e. the area shed off in bleed tubes) is essentially constant.

The propagation parameter would remain the same. However, now the continuity equation changes. The change in flow per unit length must not only store in the radially expended tube segment, but must also feed the bleed-off tubes.

Now the bleed tubes are terminated in arteriole pure resistance endings. However, they do have storage capacitance, just as did the major arterial system. The constancy of Moens-Korteweg velocity as well as direct measurement (see (14) p. 161) assures one that the elastic modules and the diameter to wall thickness ratio remains constant. This assures ability to compute the capacitance if the system volumes are known.

In the topological model, the approximate equivalent diameter system gave 25,000 tubes of 0.025 cm. diameter and 3 cm. length as attached to the main tube. The volume of the main tube is estimated as $0.25^2 \times 100 = 6$ cc., or 10 cc. rounded out. (The brachial is more like $0.785 \times .8^2 \times 100 = 50$ cc., as a cylinder, but if cut to 1/3 as a cone, it comes to 17 cc.). The next division of branch tubes has a volume of $.025^2 \times 3 \times 25{,}000 = 45$ cm. The following topological division into branch tubes is at the level of arteriols, which have a comparable volume. However, only a few percent of them are open, and likely closed at their entrance side. Thus their capacitance is negligible.

Thus the bleed system would appear to also have a distributed capacitance that acts to load the capacitance of the main tapered arterial channel. Study of (64) would suggest that the loading may be considered to represent an increased capacitance in which half the external volume per unit length is distributed along the main channel. If the external volume is about 50 cc. and the tube volume is about 10 cc, there is a loading by about a factor of 3.5. Thus the bleed

tubes can be treated as ultimately resistive, and of arteriole size, and for a first approximation, that only the arterioles themselves are attached directly to the main tube with the capacitance lumped into the main tube. Thus if one were to write for the added parallel shunting bleed flow

$$\frac{\partial Q}{\partial x} = nq = \frac{-n\pi d^4}{128\mu_o}\left(\frac{\partial p}{\partial z}\right) = \frac{-\pi d^4}{128}\, n\left[\frac{\bar{p}+p}{\ell}\right]$$

as a resistance law (because of the small size, purely resistive)

d = arteriole diameter
q = flow per arteriole
p = pressure in the artery (gage)
Z = bleed-off tube lengths
n = number of such tubes per unit length
$\bar{P}$ = mean arterial pressure
ℓ = arteriole length (nominally 20 times the arteriole diameter).

It is assumed that n is likely to be some function of arterial diameter. Thus

$$\frac{\partial Q}{\partial x} = -\left(\frac{AD'}{ES}\right)\frac{\partial p}{\partial t} - \left(\frac{\pi d^4}{128\mu_o}\right)\left(\frac{N}{L_o}\right)\left(\frac{\bar{p}}{\ell}\right)\left(1+\frac{p}{\bar{p}}\right)$$

D' = the new effective arterial elastic diameter (to reflect the distributed bleed volume)
N = total number of arterioles
L_o = length of the arterial system.

The equation set thus becomes

$$Q = -\frac{A^2}{8\pi\mu_o}\left(\frac{\partial p}{\partial x}\right)\frac{1}{F_1(Z)}$$

$$\frac{\partial Q}{\partial x} = -\left(\frac{AD'}{ES}\right)\frac{\partial p}{\partial t} - \left(\frac{\pi d^4}{128\mu_o}\right)\left(\frac{N}{L_o}\right)\left(\frac{\bar{p}}{\ell}\right)\left(1+\frac{p}{\bar{p}}\right)$$

$$Z = \frac{A}{\pi}\frac{w}{\nu}$$

$$\frac{dA}{dx} = \text{constant}$$

If Q and p are decomposed as follows:

$$Q = Q_o(x) + Q_1(x)\, e^{jwt}$$
$$p = p_o(x) + p_1(x)\, e^{jwt}$$

then the steady state solutions derive from

$$Q_o = \frac{-A^2}{8\pi\mu_o}\frac{dp_o}{dx}\frac{1}{F_1(Z)}$$
$$DQ_o = \frac{-\pi d^4}{128\mu_o}\frac{N}{L_o}\frac{\bar{p}}{\ell}$$

or

$$Q_o = \frac{\pi d^4}{128\mu_o}\frac{N}{L_o}\frac{\bar{p}}{\ell}\left(L_o - x\right)$$

(i.e. the flow tapers down to 'zero', or 'one' arteriole, having disappeared through the bleed tubes).

On the other hand, as illustrated in (1), the pressure drop remains essentially low. Thus

$$\frac{d\,p_o}{dx} \ll \frac{\bar{p}}{L_o}$$

The fluctuating portion becomes

$$Q_1 = \frac{-A^2}{8\pi\mu_o} \frac{D\,p_1}{F_1}$$

$$DQ_1 = -\left(\frac{AD'}{ES}\right) jw p_1 - \left(\frac{\pi d^4}{128\mu_o} \frac{N}{L_o \ell}\right) p_1$$

$$= -\left(\frac{AD^1}{ES}\right) jw p_1 - \frac{Q_{oo}}{\bar{p} L_o} p_1$$

Q_{oo} is the mean entrance flow for this arterial system expressed in terms of z

$$z^2 \frac{d^2 p_1}{dz^2} + \left[2 - z \frac{d \ln F_1}{dz}\right] z \frac{dp_1}{dz} - \frac{8\pi\mu_o Q_{oo}}{\bar{p} L_o \left(\frac{dA}{dx}\right)^2} F_1 \left[1 + \frac{j\bar{p} D'}{ES} \frac{\pi \nu_o L_o}{Q_{oo}} z\right] p_1 = 0$$

The elegance of this form is that it offers p_1, purely as a function of z, burying within it both the spatial, the temporal, and the damping parameter variation all in one stroke! The only complexity lies in the functional variation of F.

It is instructive to evaluate the constants, even if only in a conventional fashion. Thus choosing for the brachial system

μ_o = 0.035 poise
D = 0.8 cm
V = 50 cm/sec.
Q_{oo} = AV = 25 cc./sec.
$\bar{p}$ = 100 mm = 130,000 dynes/cm.
L_o = 100 cm.
$\frac{dA}{dx} = \frac{A}{L_o}$ = 0.0050 cm.
ν_o = 0.035 strokes
C_o = 500 cm./sec. (Moens-Korteweg propagation velocity)
$\frac{\bar{p}D}{ES}$ = 0.5 (since $Co^2 = \frac{ES}{D\rho}$)
$\frac{\bar{p}D'}{ES}$ = 3.5 x 0.5 (This is to take care of the extra bleed tube capacitance by some reasonable convention).

Then

$$\frac{8\pi\mu_o Q_{oo}}{\bar{p} L_o \left(\frac{dA}{dx}\right)^2} = 0.068$$

$$\frac{\pi\bar{p}D'}{ES} \frac{\nu_o L_o}{Q_{oo}} = 0.80$$

It is instructive to assess the likely Z range.

At the entrance

$$z = \frac{2Af}{\nu}$$

= 34 (at 1.2 cps fundamental)

= 170 (at a dicrotic wave frequency of 6 cps)

= 340 (at a 10th hormonic)

Thus

$$Z^2\frac{d^2p_1}{dZ^2}+\left[2-Z\frac{d\ln F_1}{dZ}\right]Z\frac{dp_1}{dZ}-0.068F_1+\left[1+0.8jZ\right]=0$$

At the 'exit' (single arteriole)

$$Z = 0.0008 \text{ (at a dicrotic wave frequency of 6 cps)}$$

Thus

$$Z^2\frac{d^2p_1}{dZ^2}+\left[2-Z\frac{d\ln F_1}{dZ}\right]Z\frac{dp_1}{dZ}-0.068F_1\left[1+0.8jZ\right]p_1=0$$

At low values of Z (i.e. the overdamped region $Z<1$) the equation approaches

$$Z^2\frac{d^2p_1}{dZ^2}+\left[2Z-\frac{jZ^2}{6}+\frac{17}{576}Z^3\right]\frac{dp_1}{dZ}-.068\left[1+\frac{jZ}{6}+\frac{Z^2}{1152}\right]\left[1+0.8jZ\right]p_1=0$$

$$Z^2\frac{d^2p_1}{dZ^2}+\left[2Z-.167jZ^2+.030Z^3\right]\frac{dp_1}{dZ}-.068\left[1+.97jZ-.132Z^2\right]p_1=0$$

At high values of Z (i.e. the underdamped region, $Z>100$) the equation approaches

$$Z^2\frac{d^2p_1}{dZ^2}+\left[Z+.414\sqrt{Z}-.414j\sqrt{Z}\right]\frac{dp_1}{dZ}-.068\left[\frac{j}{8}Z+\frac{\sqrt{Z}}{4\sqrt{2}}+\frac{3}{8}+\frac{j\sqrt{Z}}{4\sqrt{2}}\right]\left[1+.8jZ\right]p_1=0$$

$$Z^2\frac{d^2p_1}{dZ^2}+\left[Z+.414\sqrt{Z}-.414j\sqrt{Z}\right]\frac{dp_1}{dZ}-.068\left[-.100Z^2-.140Z^{3/2}+.117\sqrt{Z}+.375+.140jZ^{3/2}+.425jZ+.177j\sqrt{Z}\right]p_1=0$$

For the intermediate range of Z, it is more difficult to represent the laws of variation by elementary means. One should really use a number of truncated polynomial coefficients for intermediate ranges, or one could use an elaborate computer program. However, this is hardly even necessary or worth while.

Instead one may probe of the validity of this entire program by careful matching of solutions. This means that the intrinsic equations are

$$Z^2\frac{d^2p_1}{dZ^2} + 2Z\frac{dp_1}{dZ} - .068[1+jZ]p_1 = 0$$

for a range around Z = .001 (the tube termination) to some intermediate value (say stretched to somewhat beyond Z = 1)

$$Z^2\frac{d^2p_1}{dZ^2} + Z\frac{dp_1}{dZ} + .0068\,Z^2p_1 = 0$$

for a range $Z > 100$ (from conditions at the beginning of the tube, i.e. whatever is necessary for a triangular wave input.) to an intermediate value (say, somewhat below 100).

The matching of solutions required are those adjustments that will permit a smooth match in pressure and its derivative. If the question is raised whether this doesn't create extra mismatches, the answer is that the technique chosen as a whole of tapering the tube to avoid the multiple reflection problem, is being used once again as a concept of analytic continuation to piece out the intermediate range of Z with continuing solutions.

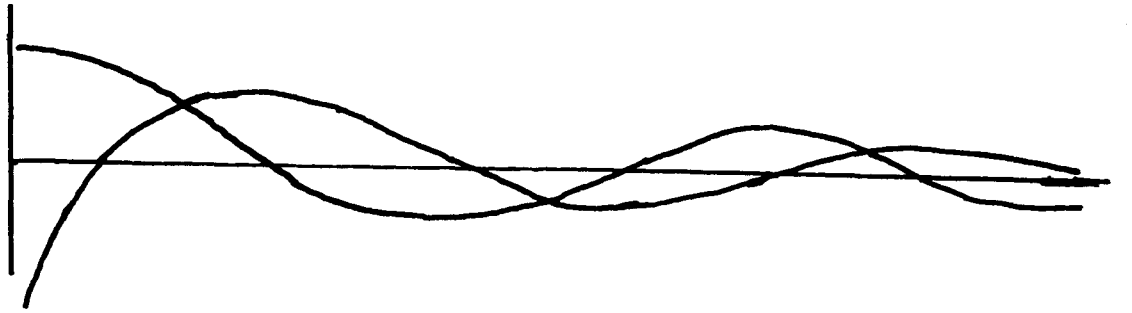
It is obvious that the high Z solution must be very nearly

$$p = AJ_0(.0825Z) + BY_0(.0825Z)$$

J_0 = Bessel function of Zeroth order

Y_0 = Bessel function of the second kind.

These solutions are shown below:



They indicate that at y = o, J_o approaches unity with no slope (i.e. the derivative equals zero) and that Y_o approaches minus infinity (i.e. as a logarithmic divergence).

For the low Z case, one must first examine the indicial equation, which comes from

$$Z^2\frac{d^2p}{dZ^2} + 2Z\frac{dp}{dZ} - .068 = 0$$

The roots of the indicial equation come from

$$m(m-1) + 2m - .068 = 0$$

$$m = 0.0625,\ -1.0625$$

Thus the beginning terms of solution are

$$p = CZ^{0.0625}\left[1 + 0.032jZ + \cdots\right] + \frac{E}{Z^{1.0625}}\left[1 - 0.54jZ + \cdots\right]$$

Now for boundary conditions. The method of satisfying the boundary conditions is to use one of the constants up for the low Z solution at the end of the tube, one of the constants for the hi Z zolution up at the beginning of the tube, and then match the two solutions at some intermediate value.

Start first from the low Z end. It is clear that if Z approached zero, rigorously E would have to vanish. However, as satisfactory a way of viewing this is to view the flow as small so that the derivative of p (proportional to flow) is small. This would make, nearly (dropping the small fractional portions of exponents)

$$p = C\left[\frac{6\times10^{-5}}{Z} + 1 + .032jZ + \cdots\right]$$

This solution was based on making the flow nearly zero at Z = 0.001, the single arteriole Z. It is clear that even down to Z = 0.001 the first term is negligible, and the third term is negligible even up to Z = 1. Thus the predominant character of the termination of the low Z end must be

$$p = C.$$

Thus the match required in an intermediate Z range is that the high Z solution should also tend to flatten off.

Here the same argument may be viewed as to the role of Y_0. The function J_0 flattens out in the 'vicinity' of y = o, namely in the vicinity of y less than 1/2 or Z less than 6. Analytic continuation is required to the vicinity of Z = 1. However, if the high Z solution were to be permitted to approach zero, the logarithmic divergence of Y_0 would govern. Thus the Y_0 solution at high Z must be the analytic continuation of the near 1/Z solution at low Z. Thus they must both vanish. Thus the only concern is with the near constant solution for p at low Z, and the Bessel function of the first kind type of solution at large Z. However at large Z, the Bessel function can be expanded as a semi-convergent descending power series in Z. (See (64), or for greater detail, see Watson (65)). Thus the solutions for the advancing and reflecting waves, which would have been written as A $J_0(y)$ + B $J_0(-y)$, are now written as

$$p = Ae^{a_0 z + a_1\sqrt{z} + a_2 \ln z + \cdots} + Be^{-a_0 z + b_1\sqrt{z} + b_2 \ln z + \cdots}$$

The first exponent $\pm a_0$ should represent the plane undamped wave portion of the solution at high enough Z.

Matched for the equation

$$z^2\frac{d^2p_1}{dz^2} + \left[z + .414\sqrt{z} - .414j\sqrt{z}\right]\frac{dp_1}{dz} + \left[.0068z^2 + .0095z^{3/2} - .012z^{1/2} - .025 - .0095jz^{3/2} - .0289jz - .012jz^{1/2}\right]p_1 = 0$$

the solutions become

$$p_1 = Ae^{.0825jz + .115(1+j)z^{1/2} - .365\ln z + \frac{.108(1-j)}{\sqrt{z}}} + Be^{-.0825jz - .115(1+j)z^{1/2} - .634\ln z + \frac{.022(1-j)}{\sqrt{z}}}$$

At low values of Z, the solutions approach

$$p = cz^{.0625}\left[1 + .032jz + \cdots\right]$$

which is basically zero.

Thus the concern is with analytic continuation of the high Z solution to a low value.

Investigation indicates, as before, that even at intermediate values of Z, the return wave (-.0825 j Z ..) is sufficiently attenuated to be considered negligible, and thus effectively B = 0.

Consider now transforming the remaining solution. At the entrance, for the fundamental there is a base value of Z. Call this Z_o. As computed previously, this was about $Z_o = 34$

(D = 0.8 cm, = 0.035 stokes, f = 1.2 cps)

The variation of Z with fractional length X (i.e fraction of 100 cm.) and frequency F relative to the fundamental is given by

$$Z = Zo\ F\ (1 - X)$$

The total time dependent solution for pressure thus becomes

$$p = \sum_{f=1}^{n} A_f \left[\frac{e^{.115\sqrt{fZ_o}\,(\sqrt{1-x}\,-1) + \frac{.108}{\sqrt{fZ_o}}\left(\frac{1}{\sqrt{1-x}}-1\right)}}{(1-x)^{.365}}\right]$$

$$\sin\left[fwt + .0825 fZ_o(-x) + .115\sqrt{fZ_o}\,(\sqrt{1-x}\,-1) - \frac{.108}{\sqrt{fZ_o}}\left(\frac{1}{\sqrt{1-x}}-1\right)\right]$$

where A_f should be the Fourier coefficients for the input, say the triangular pressure wave input. Thus

$$A_f = \frac{2}{\pi} \quad \frac{A(-1)^f}{f}$$

for the Fourier sin F wt series.

Thus the first concern is with how the relative amplitudes vary down the tube. For this purpose, the numbers need only be regarded as conventional, i.e. the fundamental of 1.2 cps can be regarded as being 1 cps so that f itself represents nearly frequency in cps, etc.

The relative amplitudes and phase lag of each harmonic down the tube is given approximately in the following table.

Amplitude and Phase Lag for a
Tapered Arterial Tube

(Diameter = 0.8 cm; length = 100 cm.; fo $\approx$ 1 cps)

Harmonic Amplitude (relative to the input harmonic amplitude)-A;
and Phase Lag-B(radians)

Frequency - cps.

Distance cm.	1		2		3		4		6		8		10	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
0	1	0	1	0	1	0	1	0	1	0	1	0	1	0
30	.90	1.0	1.01	1.8	.98	2.7	.95	3.6	.90	5.3	.86	7	.83	9
60	.79	1.9	.99	3.7	.92	5.4	.86	7.2	.76	11	.70	14	.65	18
90	.66	3.0	1.24	5.7	1.07	8.3	.95	11	.77	16	.64	21	.55	27
100	0	-	0	-	0	-	-	-	-	-	-	-	-	-

Triangular wave amplitudes
(for unity triangular wave)

0	-.64	.32	-.21	.16	-.11	.08	-.06

Note, that many values have been extended past their convergence range in Z. However, it is not believed that the basic details are incorrect. The results for a tapered tube with bleed flow show:

a. The harmonic amplitudes hold their magnitude with little damping down the tube (however, the reflected wave was so much more highly attenuated as to be negligible);

b. The higher frequencies are selectively attenuated more (almost linearly decaying in amplitude at 16 cps, the dichrotic notch frequency).

c. The decay in amplitude tends to take place rather precipitiously out near the end of the tube.

d. The distortional wave form down the tube does not arise from 'standing waves' but from the selective phase shift accompanying the relative damping associated with the changing damping factor Z. Specifically, the distortion accentuates the second to fourth harmonic to give the impression of a standing wave resonance.

In summary, thus, the questions and proposals that were made in (1) on cardiovascular dynamics has come to flower. The present model, while apparently geometric, is *not*. It is *really topological*. It shows that the act of flow branching, while maintaining a near constant mean velocity, represents a diminution of area, and thus basically a diminution in Z. However, the termination always continues to look resistive regardless of the level of division, and the arterial branch continues to look capacitative. The consequences of this have been shown to damp the system, to preferentially damp higher frequency to show the equivalence of standing waves, and to demonstrate what appears to be a mild resonance at a dicrotic wave frequency.

IX. BIBLIOGRAPHY

1. A. S. Iberall, S. Z. Cardon "Analysis of the Dynamic Systems Response of Some Internal Human Systems", three quarterly reports, July 1963, December 1963, April 1964, NASA Contract No. NASW-678, NASA Office of Space Sciences, Washington, D. C.

2. B. Goodwin TEMPORAL ORGANIZATION IN CELLS, Academic Press, 1963.

3. M. Calvin "The Origin of Life on Earth and Elsewhere II", U. California - Berkeley, UCRL - 9440, Oct. 19, 1960.

4. B. Clegg "A Two-Sensor, Lumped Parameter Model of Human Respiratory Regulation", Case Institute of Technology, December 1963.

5. C. Best, N. Taylor THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE, Williams and Wilkins, 1961.

6. N. Minorsky NON-LINEAR OSCILLATIONS, Van Nostrand, 1962.

7. A. S. Iberall "Study of an Electronic Timer", February 1962, Contract No. DA-49-186-ORD-1052, Diamond Ordnance Fuze Laboratory, Washington, D.C.

8. R. Rushmer CARDIOVASCULAR DYNAMICS, Saunders, 1961.

9. A. Guyton TEXTBOOK OF MEDICAL PHYSIOLOGY, Saunders, 1961.

10. A. S. Iberall Trans ASME Series D, J. Basic Engin., March 1960, Vol. 82(1) p. 96-112 (Parts 1-2); Sept. 1960, Vol. 82(3), p.513 (Part 3).

11. B. Zweifach "The Microcirculation of the Blood", Scientific American, Jan. 1959, p. 2-8.

12. M. Wiedeman "Dimensions of Blood Vessels from Distributing Artery to Collecting Vein", Circ. Res. Vol. 12, No. 4, Jan.-June 1963, p.375.

13. J. Grant AN ATLAS OF ANATOMY, Williams and Wilkins. 1947.

14. D. McDonald BLOOD FLOW IN ARTERIES, Arnold, 1960.

15. A. Grafflin, E. Corddry "Studies of Peripheral Blood Vascular Beds in the Bulbar Conjunctiva of Man", Bull. of John Hopkins Hosp., Vol. 43 p. 275, 1953.

16. VASCULAR PATTERNS AS RELATED TO FUNCTION, Second Conference on Microcirculatory Physiology and Pathology, April 5, 1955; Williams and Wilkins, 1955.

17. D. Patel, F. DeFreitas, J. Greenfield, D. Fry "Relationship of Radius to Pressure Along the Aorta in Living Dogs" J. Appl. Physiol., 18, p. 1111, Nov. 1963.

18. N. Suwa, T. Niwa, H. Fukasuwa "Estimation of Intravascular Blood Gradient by Mathematical Analysis of Arterial Casts", Tohoku J. Exper. Med., Vol. 79, No. 2, p.169-198, March 25, 1963.

19. S. Sarnoff, J. Mitchell "The Regulation of the Performance of the Heart", Am. J. of Med., Vol. 30, No. 5, p.747, May 1961.

20. E. Bloch "A Quantitative Study of the Hemodynamics in the Living Microvascular System", Am. J. Anat. Vol. 110, No. 2, March 1962, p.125.

21. T. Ruch, J. Fulton MEDICAL PHYSIOLOGY AND BIOPHYSICS, Saunder, 1961.

22. I. Page, F. Bumpus, H. Schwartz "Angiotensin", Sci. Amer.,March 1959, p.54.

23. W. Montagna, R. Ellis BLOOD VESSELS AND CIRCULATION Advances in Biology of Skin, Vol. 2, 1960 Brown University Symposium Proceed., Pergamon, 1961.

24. A. S. Iberall "Mathematical Modelling for the Mortality Effects of Various Radiation Dosage Schedules" Three reports, July 1963,August 1963,February 1964. AEC Contract No. AT(11-1)-1254, Atomic Energy Commission, D. C.

25. E. Gordon, M. Goldberg, G. Chosy "A New Concept in the Treatment of Obesity", J. Am. Med. Assoc., Vol. 186, Oct. 5, 1963, p.50.

26. L. Newburgh "Obesity. I. Energy Metabolism", Physiol. Rev. Vol. 24, 1944, p.18.

27. L. Carlson "Man in Cold Environment, a Study in Physiology", Arctic Aeromedical Laboratory, Contract AF 33(038)-422, Aug. 1954, USAF.

28. J. R. Marshall, C. H. Lambertson, "Interactions of Increased pO_2 and pCO_2 Effects in Producing Death in Mice", J. Appl. Physiol. 16, 1 (1961).

29. H. Barcroft, H. Swan, SYMPATHETIC CONTROL OF HUMAN BLOOD VESSELS, Arnold,1953.

30. F. R. Griffth, Jr., "Fact & Theory Regarding the Calorigenic Action of Adrenaline"., Physiol. Rev. 31, 151 (1951).

31. L. Lundholm, "The Mechanism of the Vasodilator Effect of Adrenaline" I. The Effect on Skeletal Muscle, Acta Physiol. Scand., 39, Suppl. 133, 3, (1956).

32. S. Hilton, "Local Mechanisms Regulating Peripheral Blood Flow", Physiol. Rev., 42, Suppl. 5, 265 (1962).

33. J. Axelrod, Symposium on ULTRASTRUCTURE AND METABOLISM OF THE NERVOUS SYSTEM, Williams & Wilkins, Baltimore, 1962.

34. G. Burnstock, M. E. Holman and C. L. Prosser, "Electro Physiology of Smooth Muscle", Physiol. Rev., 43, 482 (1963).

35. C. Hyman, R. L. Paldino and E. Zimmermann, "Local Regulation of Effective Blood Flow in Muscle". Circulation Res., 12, 176 (1963)

36. G. E. Anderson, R. W. Hillman, Izak F. A. Van Elk, A. John Perfetto "Postabsorptive Undulations and Oscillations in Blood Glucose", Amer. J. of Clin. Nutrition, 4, 673 (1956).

37. A. Krogh, THE ANATOMY AND PHYSIOLOGY OF CAPILLARIES, Yale U. Press, New Haven, 1922.

38. S. Thomas in HORMONES AND THE KIDNEY, Edited by P. S. Williams, Academic Press, 1963.

39. O. H. Gauer, J. P. Henry, "Circulatory Basis of Fluid Volume Control" Physiol. Rev., 43, 423 (1963).

40. S. P. Asper, Jr., H. A. Selenkow, & C. A. Plamondon , "Comparison of Metabolic Activities of 3, 5, 3^1- L - Triiodothyronine and L - Thyroxine in Myxedema". Bull. Johns Hopkins Hospital, 93, 164 (1953).

41. R. E. Logan and A. Lein, "Time Required for Metabolic Response Single Injections of Thyroxin", Fed. Proc. 10 85 (1951)

42. R. W. Rawson, J. E. Rall, O. H. Pearson, J. Robbins, H. F. Poppell and C. D. West, "L-Triiodothyronine Versus L-Thyroxine, A Comparison of their Metabolic Effects in Human Myxedema", Am. J. Med. Sci. 226, 405 (1953).

43. G. Duncan DISEASES OF METABOLISM, 4th Edition, Saunders, N. Y. 1959

44. L. Van Middlesworth and A. P. Intoccia, "Metabolism of Dietary Iodine as Revealed by I^{131} Balance Studies" Metabolism 6, 1 (1957).

45. C. W. Lloyd and J. Lobotsky GLANDULAR PHYSIOLOGY AND THERAPY, 5th Edition. Amer. Med. Assoc., Chicago,1954.

46. F. Gross and P. Lichtlen "Further Evidence for a Qualitative Difference between Aldosterone and Cortexone", ALDOSTERONE, Edited by Alex F.Muller and Cecilia M. O'Connor, Little Brown & Co. Boston, 1958.

47. M. B. Lipsett, I. L. Schwartz, and N. A. Thorn "Hormonal Control" MINERAL METABOLISM, Vol 1, Part B, Chap. 12, Academic Press, 1961.

48. F. L. Hoch, "Biochemical Actions of Thyroid Hormones", Physiol. Rev. 42, 605 (1962)

49. R. J. Wurtman, I. J. Kopin and J. Axelrod, Thyroid Function and the Cardiac Disposition, Endocrinology, 73, 63 (1963).

50. L. Danziger and G. L. Elmergreen, Bull. of Math. Biophys., 16, 15 (1954) 18, 1 (1956) 19, 9 (1957).

51. R. Pitt-Rivers and J. R. Tata, THE THYROID HORMONES, Pergamon Press, London (1959)

52. B. S. Andersson, S. M. McCann "A Further Study of Polydipsia Evoked by Hypothalamic Stimulation of the Goat."Acta Physiol. Scand.,33, 333 (1955).

53. S. Arieti, AMERICAN HANDBOOK OF PSYCHIATRY, Vol. 2, Basic Books, 1959.

54. J. Frenkel, WAVE MECHANICS, ELEMENTARY THEORY, Dover 1950.

55. R. Coles "Terror-Struck Children" New Republic, May 30, 1964.

56. R. Munroe, SCHOOLS OF PSYCHOANALYTIC THOUGHT, Dryden Press, 1955.

57. M. Klein, P. Heimann, R. Money-Kyrle, NEW DIRECTIONS IN PSYCHO-ANALYSIS, Basic Books, 1955.

58. A. S. Iberall, "Philosophy for Mid-Twentieth Century Man", unpublished document, 1957.

59. H. S. Sullivan, THE INTERPERSONAL THEORY OF PSYCHIATRY, Norton, 1953.

60. D. Levy,"A Note of Pecking in Chickens', Psychoanalytic Quart., 4, 612 (1935) "On Instinct-Satiation! An Experiment on the Pecking Behavior of Chickens", J. Gen. Psych., 18, 327 (1937).

61. THE COLLECTED WORKS OF KAREN HORNEY, Vol. 1, 2. Norton, 1937-1950.

62. F. Alexander,DYNAMIC PSYCHIATRY, U. of Chicago, 1952; PSYCHOSOMATIC MEDICINE, Norton, 1950.

63. S. Arieti,INTERPRETATION OF SCHIZOPHRENIA, Brunner, 1955.

64. A. S. Iberall, "Attenuation of Oscillatory Pressures in Instrument Lines", NBS J. Res., 45, July 1950, p. 85.

65. G. Watson, A TREATISE ON THE THEORY OF BESSEL FUNCTIONS, Cambridge,1952.

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